DISCOVERIES MAGAZINE

VOLUME 12 — 2023

LOOKING PAST OUR FUTURE

The ongoing transformation of our campus, our institution and our health system

P.23

UC San Diego
HEALTH SCIENCES

Contributors

John M. Carethers, MD
Vice Chancellor
Health Sciences

Patricia Maysent
Chief Executive Officer
UC San Diego Health

Editors
Scott LaFee
Nicole Mlynaryk

Writers
Michelle Brubaker
Yadira Galindo
Liezel Labios
Corey Levitan
Jeanna Vazquez

Photographers
Kyle Dykes
Erik Jepsen

Publication Design
Traina

UC San Diego Health Sciences comprises the region's only academic health system, one of the nation's top research-intensive schools of medicine, the Herbert Wertheim School of Public Health and Longevity Science and the Skaggs School of Pharmacy and Pharmaceutical Sciences.

On the Cover

With lofty visuals and airy flair, artist Mike Campau visualizes UC San Diego's recent past and future plans for the La Jolla and Hillcrest health campuses, both of which have undergone and will continue to undergo dramatic change to meet the needs and demands of 21st-century health sciences, education and clinical care.

"Science is a way of life. Science is a perspective. Science is the process that takes us from confusion to understanding in a manner that's precise, predictive and reliable — a transformation for those lucky enough to experience it that is empowering and emotional."

BRIAN GREENE,
THEORETICAL PHYSICIST

ONE NEEDN'T GAZE AT THE HEAVENS OR PONDER the elusive manifestations of string theory (Greene's specialty) to see science and transformation at work. It happens every day at UC San Diego across its missions of education, research and clinical care. It is a familiar way of life, an honored perspective and an ongoing process.

This year, transformation is a theme of *Discoveries*, which takes shape and purpose in different and diverse ways in health sciences—perhaps most obviously in the form of buildings and infrastructure that have arisen over the past decade or so on the La Jolla health campus, east of the main university, and will do so in the next two decades in Hillcrest, where a $3 billion long-range development plan envisions a new hospital, an outpatient pavilion, housing and expansive community resources. Check out the foldout for more details.

Elsewhere in the magazine, you can read about transformation in the reimagining of public health in the 21st century, led by faculty, staff and students at the Herbert Wertheim School of Public Health and Human Longevity Science; dramatic advances in organ transplantation; the increasing use of artificial intelligence in both research and clinical care; evolving clinical trials; and the human microbiome in health care.

People effect change, and change affects people. In 2022, David A. Brenner, MD, stepped down as vice chancellor for Health Sciences (and former dean of the School of Medicine) after 15 years of unprecedented service. His successor, John M. Carethers, MD, returns to UC San Diego to officially assume the post this month. Both men are profiled in this issue.

Change often requires a catalyst, something to transform ideas into reality. Such was the decade-long Campaign for UC San Diego, which concluded in July 2022 after raising an astounding $3.05 billion from more than 164,000 individuals, foundations and corporations, including $100 million from Joan and Irwin Jacobs to help build the Jacobs Medical Center; $350 million from T. Denny Sanford to support stem cell research and establish an eponymous institute to study and promote empathy and compassion; $50 million to create the Epstein Family Alzheimer's Research Collaboration with the University of Southern California; $25 million to found the Herbert Wertheim School of Public Health; and $10 million each from Darlene Shiley to expand Shiley Eye Institute, from the Price Philanthropies and the Price family to support the Hillcrest redevelopment, and from Leo and Emma Zuckerman to revitalize emergency services at Jacobs Medical Center.

This issue of *Discoveries* is a look at what was, is and will be, a snapshot of the students, staff and faculty at UC San Diego whose transformative talents and ambitions have changed and are changing lives for the better.

Sincerely,

SCOTT LAFEE
EDITOR

Features

54
Pharming the Microbiome

BY SCOTT LAFEE

04 →

Socially Justified Health Care

Treating the whole patient — body, mind and spirit — means physicians need to understand who they are and where they come from. It's a two-way conversation: intentional, explicit and compassionate.

BY JEANNA VAZQUEZ

30 →

(Re)introducing John

Transformation continues under the leadership of the new vice chancellor for Health Sciences, John M. Carethers.

BY NICOLE MLYNARYK

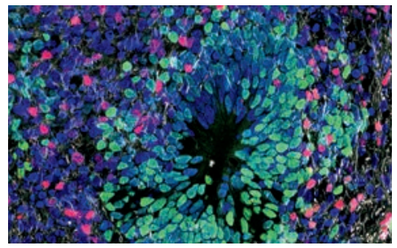
Articles

14 →

Stopping Cancer Before It's Cancer

Pre-Cancer Genome Atlas seeks telltale predictors of disease to come.

BY COREY LEVITAN



← 68

Organ Match

Can you tell the difference between a brain organoid and one mimicking a lung? Take our quiz.

BY SCOTT LAFEE

↑

The gut microbiome plays a critical but poorly understood role in how drugs work or don't work in the body. It also presents therapeutic possibilities unto itself.

SOCIALLY JUSTIFIED HEALTH CARE

BY JEANNA VAZQUEZ

IN MEDICINE, TREATING THE WHOLE PATIENT — body, mind and spirit — is a primary goal for physicians who seek to become comprehensive providers of care. As part of that effort, UC San Diego School of Medicine is developing a curriculum that provides real-world training and education, this includes creation of the Social Justice Curriculum, which trains residents with an anti-oppression emphasis rooted in empathy and compassion.

"When health care is not conducive for a patient or their lifestyle, it can lead to health inequities," said **Megha Shankar, MD**, primary care physician at UC San Diego Health and assistant professor of medicine at UC San Diego School of Medicine. "As primary care physicians, we need to understand a person's social determinants of health and provide them with the best options that work for their specific circumstance."

Social determinants can range from whether a patient has the resources to obtain medication refills to analyzing housing and neighborhoods to determine whether environmental factors are contributing to health problems.

The curriculum covers six topics: refugee health, homeless medicine, correctional health, senior care, environmental justice and trauma-informed care.

The two-year program launched in July 2022. Lectures and workshops are coupled with field visits to relevant facilities, such as domestic violence shelters, correctional facilities, community centers and underserved neighborhoods. Over the course of the curriculum, residents will experience hands-on training during half-day sessions for each topic.

"These extra educational experiences are necessary for residents," said **Stacy Charat, MD**, associate professor of medicine at UC San Diego School of Medicine.

Presence of Five Racial Justice Framework

1.

Prepare with intention: Reflect on identity, bias and power dynamics, and create structures to address bias and structural determinants of health.

2.

Listen intently and completely without interruption: Listen deeply for the potential impact of anti-Black racism on patient health and interactions with health care.

3.

Agree on what matters most: Have explicit conversations about patient goals, treatment comfort and consent, and referral planning.

4.

Connect with the patient's story: Acknowledge socioeconomic factors influencing patient health and focus on positive efforts.

5.

Explore emotional cues: Notice and name patient emotions, and consider how experiences with racism might influence emotions.

"They provide training outside of traditional health care systems and assist residents in understanding what community resources are available for their patients.

"For example, at the correctional health tour, residents tour the facility and shadow providers who care for incarcerated individuals. In turn, this provides unique training on both primary and mental health care."

Shankar said she realized there was a need for social justice health care training during her own residency program.

"I did a primary care track when I was in training, and I appreciated its focus," said Shankar. "However, I wish I could have focused on social determinates of health and how to address health inequities. So, that's what we're doing here."

To ensure the program is addressing current needs and interests of medical trainees, Shankar and Charat partnered with residents and medical students to develop the curriculum for each social justice topic.

"The curriculum I'm helping develop is specific to trauma-informed care," said Megan King, a second-year medical student and research assistant. "In the literature, there are qualitative studies on communication practices involving trauma, domestic violence, gender identity and LGBTQ care. I use these studies to create an evidence-based training guide for the residents and coordinate the adjoining half-day tour as well."

The training guide is based on the Presence of Five Racial Justice Framework, developed by Shankar with colleagues at Stanford University. The multiphased project emphasizes human-centered design thinking and community-based research principles, Shankar said.

The five elements of the framework, originally created for anti-racist communication with Black patients, are as follows:

- **Prepare with intention:** Reflect on identity, bias and power dynamics, and create structures to address bias and structural determinants of health.
- **Listen intently and completely without interruption:** Listen deeply for the potential impact of anti-Black racism on patient health and interactions with health care.
- **Agree on what matters most:** Have explicit conversations about patient goals, treatment comfort and consent, and referral planning.
- **Connect with the patient's story:** Acknowledge socioeconomic factors influencing patient health and focus on positive efforts.
- **Explore emotional cues:** Notice and name patient emotions and consider how experiences with racism might influence emotions.

"This curriculum is about training physicians to make patients feel more comfortable in a way that is evidence-based and does not re-traumatize them," said King. "In this instance, it's not about conveying clinical knowledge: it's about understanding patients' life experiences and being able to tap into the softer, interpersonal aspect of medicine."

The Social Justice Curriculum is intended to elevate patient care beyond the clinic and bedside. It is available to all second- and third-year residents in the primary care pathway.

"This will positively impact patient care because residents and future physicians will be more adept at screening patients for specific scenarios," said Shankar. "We're addressing the needs of individuals from underserved communities to ensure our physicians are thinking critically about how a patient's life impacts their overall health." ●

↑ **Megha Shankar, MD**

WELL

Sensors on the skin, such as electrode-equipped temporary tattoos or patches that emit ultrasound waves, promise a future of on-the-spot, on-the-go health monitoring.

WORN

BY LIEZEL LABIOS

WHEN YOU HEAR THE WORD *WEARABLES,* devices such as smartwatches or Fitbits most likely come to mind. These wearables have become a part of everyday life, allowing you to, among things, count calories and steps, monitor heart rate and track sleep quality — all on your wrist. But what if a whole new world of health-related services was within reach?

At the UC San Diego Center for Wearable Sensors, engineers and clinicians are coming together to develop a new generation of wearables that can do so much more than those at hand.

They are creating advanced technologies and systems that will allow people to monitor individual health conditions at home and on the go, without consciously thinking about it. These wearables don't look anything like today's electronic gadgets. They are soft, stretchy, incredibly thin and lightweight, similar to a Band-Aid but sturdy enough to cope with the wear and tear of everyday use.

"Our goal is to help people get information about their health, fitness and medical status anytime, anywhere, simply by wearing a stamp-sized patch on the surface of the skin," said **Joseph Wang, PhD**, professor of nanoengineering at UC San Diego Jacobs School of Engineering and director of the Center for Wearable Sensors.

"Our vision is to make wearable devices that are so unobtrusive, so invisible that users are virtually unaware that they're wearing them," added center co-director **Patrick Mercier, PhD**, professor of electrical and computer engineering. "These 'unawareables' can be seamlessly integrated into daily life to acquire useful health data and users won't have to do anything."

Achieving these goals is made possible by interdisciplinary partnerships across campus.

"Our collaborations with medical researchers and clinicians have given us invaluable insight to better tailor and translate these wearables for clinical use," said Wang.

Needle-free glucose monitoring

ONE WEARABLE making the leap from lab to real-world use is a temporary tattoo that serves as a glucose monitor. Developed by a

↑ **Joseph Wang, PhD**

↑ **Brady Huang, MD**

↑ **Edward Chao, DO**

team of engineers led by Wang and Mercier, the tattoo offers diabetes patients a way to test their blood glucose (blood sugar) levels without the traditional needle-prick.

"Drawing blood is uncomfortable. No one likes doing it. The beauty of this technology is that it is a truly noninvasive means to measure glucose over the course of the day," said Mercier. "By giving this real-time information to patients, they can manage their consumption of sugars and injections of insulin much better than with periodic spot measurements."

An estimated 37 million people in the United States live with diabetes. Monitoring blood glucose levels is integral to managing their condition. Currently, patients must produce a drop or two of blood from a fingertip needle-prick multiple times per day to analyze glucose levels. Continuous glucose monitors exist, but they require inserting a needle into the abdomen or arm. Many patients avoid testing or do not do it regularly because they find it unpleasant or difficult to perform. According to **Edward Chao, DO**, clinical professor of medicine at UC San Diego School of Medicine and a physician at VA San Diego Healthcare System, one-quarter of persons receiving insulin treatment either infrequently or never test their blood glucose. Another 65 percent who use other drugs to treat diabetes test just once a month or less.

"Adherence to chronic disease management is typically low — about 50 percent. Diabetes is no exception," said Chao. "And there's a lot more self-management involved in diabetes beyond using needles to test blood glucose. A tool like the glucose-monitoring tattoo can reduce discomfort or inconvenience to increase vital monitoring."

Monitoring Glucose Levels

37M±

people in the United States live with diabetes

1/4

of persons receiving insulin treatment either infrequently or never test their blood glucose

65%

who use other drugs to treat diabetes test just once a month or less

Sources:
Centers for Disease Control, Third National Health and Nutrition Examination Survey

The tattoo is worn just like a kid's temporary tattoo: Applied to the skin with a dab of water and the backing peeled away. The tattoo contains two electrodes that apply a minute and imperceptible electrical current, generated by a small, low-power electronic circuit that connects to the tattoo. The current forces fluid between skin cells, called interstitial fluid, to rise to the surface, carrying glucose molecules along with it. A sensor in the tattoo measures the strength of the electrical charge produced by glucose to determine a person's overall glucose level.

The tattoo recently completed a Phase I clinical trial, headed by Chao, in collaboration with Wang and Mercier. The study, which took place at UC San Diego Altman Clinical and Translational Research Institute, validated the device's accuracy at detecting glucose levels compared to a traditional glucometer.

The study consisted of a small group individuals with diabetes. Each individual wore a tattoo and had their glucose levels checked after a period of fasting, and then multiple times every couple of hours after eating. The tattoo's readings were similar to results from simultaneous finger-prick glucose readings.

The research team is now refining the technology for continuous glucose monitoring, and planning for a larger second trial.

"Reactions to this technology have overall been enthusiastic," said Chao. "There can be this perception of technology being impersonal or requiring specialized knowledge to use. With a wearable like this, we have a way to personalize technology, make it more accessible and less intimidating, and even encourage patient engagement."

Sensing deeper with ultrasound

WEARABLES HAVE THE POTENTIAL TO CHANGE NOT just how patients manage chronic disease, but also how clinicians treat those patients.

Sheng Xu, PhD, professor of nanoengineering, seeks to develop wearables that go beyond what other devices can measure. "Wearable devices have so far been limited to sensing signals either on the surface of the skin or right beneath it," he said. "But this is basically just scratching the surface. There are a lot of other signals going on way below the surface. My vision is to develop wearables that can sense these signals in a noninvasive manner."

Xu integrates ultrasound technology into wearable devices. While sensors in other wearables cannot penetrate more than a centimeter below the skin, Xu's ultrasonic sensors are able to travel at least four centimeters into the body, approximately 1.5 inches. Newer versions can go as deep as 14 centimeters or more than five inches.

Deep-sensing wearables enable clinicians to do real-time, continuous monitoring of internal vital signs and physiological signals originating in deep tissues and critical organs, such as the heart, without performing invasive procedures.

For example, Xu and colleagues have created a soft, flexible stick-on patch, roughly the size of a nickel, to measure central blood pressure, or CBP. Not to be confused with blood pressure measured by a simple cuff, CBP is the pressure found inside the body's central vessels that carry blood directly from the heart to major organs. It provides information about pressures affecting the lung, heart and kidneys. CBP must be continuously monitored in patients who are in intensive care or undergoing surgery, but current clinical methods require a catheter to be inserted through the arm, groin or neck and guided into the heart.

Xu's patch does a similar job from the surface of the skin. It can be worn on the side of the neck or other body surfaces near the carotid artery or jugular vein. Embedded in the patch are tiny electronics that emit ultrasound waves into the body. When the waves bounce off a blood vessel and return to the patch, the time difference between when the waves return from the near and far walls of the blood vessel is measured, providing an indicator of the vessel's diameter. Changes in that diameter as the blood pulses through are translated into CBP.

"This technology lends itself well for long-term CBP monitoring in the hospital," said **Brady Huang, MD**, assistant clinical professor of radiology at the School of Medicine and a radiologist at UC San Diego Health. "To do that continuously and noninvasively with just a small wearable patch is pretty spectacular."

Huang, who served as the ultrasound coach and clinical advisor for the project, sees other potential clinical benefits as well.

First, the approach could make ultrasound more portable, allowing for greater use in smaller clinics or those in rural or remote locations. It could provide greater opportunities to provide ultrasound at the point of care.

Second, a stick-on patch would make ultrasound less dependent upon the operator. "In the clinic, a human operator is required to maintain contact between the ultrasound probe and the patient. The concept of a 'set it and forget it' wearable is great here because then you could monitor the patient for an indefinite period without needing a sonographer or a physician to stand there and keep the probe on the patient the whole time," said Huang.

The ultrasound patch is not yet ready for primetime. In its current state, the patch needs to be connected to an external power source, a data processor and other benchtop equipment. A startup company that Xu co-founded, called Softsonics, seeks to develop a wireless system and further refine the technology for clinical translation.

On campus, Xu and Huang continue to collaborate. They are currently working on a patch capable of ultrasound imaging of organs, such as the heart.

"We are truly going deeper with our wearable technology. There's so much more we can do from the surface of the skin," said Xu. "As I always say, the best is yet to come." ●

EQUITY THROUGH EDUCATION

BY NICOLE MLYNARYK

← Austin Marshall, MD, (center) and his PRIME-HEq classmates celebrated Match Day 2022.

↓ Native American medical students and faculty participate in an annual American Indian Blessing Ceremony and Blanket Presentation.

To support diversity and address disparities in health care, change starts with medical training.

WHEN AUSTIN MARSHALL, MD, MPH, REFLECTS ON HEALTH CARE ISSUES FACING THE LGBTQ COMMUNITY, he says many begin in the doctor's office. They're in the questions asked or not asked, the information shared or kept to oneself. Stereotypes and stigmas still affect queer people seeking medical care — something Marshall has experienced firsthand as a gay man. It wasn't until he volunteered at an LGBTQ clinic during college that he finally saw what equitable health care for this community could really look like.

"When you have providers who understand you, that bond makes you feel so much more comfortable sharing information about your life and heath," Marshall said. "It's those details that often make the difference between a generic recommendation and an effective health solution."

Personal experience drew Marshall to UC San Diego School of Medicine's Program in Medical Education (PRIME), which focuses on health equity (HEq). PRIME-HEq is one of several growing programs at UC San Diego aimed at addressing health disparities and supporting diversity within the medical profession.

"When I read the mission of the program, it immediately resonated with me," Marshall said.

PRIME-HEq trains medical students to provide competent and compassionate care to underserved populations. These students are part of the larger medical school program but complete specialized coursework on the cultural and sociopolitical factors that influence health.

PRIME students also lead outreach projects and learn strategies for developing community-based intervention programs. As part of his training, Marshall partnered with the San Diego LGBT Community Center in Hillcrest to assess local health care needs. Through these hands-on experiences, he learned more about hormone therapy, HIV testing and care, and how mental illness and homelessness affect health in the queer community.

Another hallmark of the program is that students complete a master's degree in addition to their four years of medical school. Like many of his peers, Marshall chose to pursue his degree in public health. This allowed him to complete a thesis on the mental health care needs of older LGBTQ adults, many of whom have experienced significant discrimination and loneliness since the AIDS epidemic of the 1980s. To Marshall, this public health education has been invaluable in preparing him to lead change in and out of the clinic.

"It's really useful to understand the larger structures that we practice in," he said. "When I'm trying to get my patient medication for HIV, for example, it's important for me to know what issues might come up on the backend and how I can help address them."

PRIME-HEq previously funded master's studies, but thanks to persistent advocacy from faculty and students, the 2021 California state budget included a major increase in support for PRIME programs, whose students now receive a $20,000 scholarship for each of their five years of coursework, totaling $100,000 in financial support.

"One of our goals for the additional funding is to reduce the debt burden students incur from pursuing a medical degree," said **Luis Castellanos, MD, MPH**, director of PRIME-HEq at UC San Diego School of Medicine, who noted that many PRIME students pursue primary care specialties that do not pay as much as other medical subspecialties, making it especially important to reduce their debt load.

Most PRIME students are also from backgrounds underrepresented in the medical fields. As Marshall pointed out, "If you want to recruit more underserved individuals into medical school, you need to create the social and financial support necessary for them to thrive."

↑ PRIME-TIDE has welcomed its inaugural class of medical students training to provide health care to Native populations.

After all, he said, many of the most valuable parts of his education came from his PRIME-HEq peers.

"The students are really one of the program's biggest strengths," Marshall said. "Everyone has experience and expertise in serving different communities, so we're constantly learning from and inspiring each other."

PRIME students often take on leadership roles within the student community, where they further supervise their peers. As the president of LGBTQ-PhaM, Marshall oversaw several student programs, including National Coming Out Day and Transgender Week of Visibility.

"Medical school is really challenging, and it's easy to lose sight of why you started in the first place. But to be supported by peers who can relate to your experiences and who care about the same issues really amplifies your drive and reminds you what you're fighting for."

Changing tides

ALONG WITH THE EXPANSION OF PRIME-HEQ the state budget also funded two new PRIME programs focused on the needs of Native American and Black communities. UC San Diego School of Medicine was selected to host the new program, called

Transforming Indigenous Doctor Education (PRIME-TIDE), in partnership with UC Davis. The initiative will help address the relative shortage in physicians providing health care to Native American populations.

"As a land-grant institution, we have an obligation to promote greater inclusion of American Indian students in medicine, and support the health care of our local tribes," said **Michelle Daniel, MD**, vice dean for medical education at UC San Diego School of Medicine.

UC San Diego welcomed its first class of PRIME-TIDE students in the fall of 2022. In addition to the standard medical school curriculum, these students participate in research, outreach and advocacy programs that interface with local Native American organizations. They also focus their clinical rotations on health issues that disproportionately affect these communities, including obesity, diabetes, heart disease, mental illness and substance abuse.

PRIME-TIDE is also developing mentorship programs so that each incoming student is paired with a Native American faculty member and a student further along in the program to provide social support during their medical training.

"It's just so fun and rewarding to work with these students," said **Matthew Allison, MD, MPH**, director of the PRIME-TIDE program and member of the Chickasaw Nation. "We're really excited to build more opportunities for them to grow as physicians and better serve these communities. I can't wait to see how this program evolves over time."

↑ **The California Medicine Scholars Program launched in 2022 with the help of Ramón Hernandez, DrPH (far right), and the California Medicine Task Force.**

Paving the way

WHILE PRIME SUPPORTS STUDENTS ALREADY admitted to medical school, additional structures are needed to help disadvantaged students even earlier in the academic pipeline. Through the new California Medicine Scholars Program (CMSP), UC San Diego is helping community college students from underserved regions pursue medical education.

"We know a higher proportion of Latino, Black and Native American students use the community college pathways, and have a higher intent to serve minority communities through their careers," said **Ramón Hernandez, DrPH, MPH,** member of the CMSP Founding Advisory Board. "By helping these students pursue medical school, we can simultaneously diversify the physician workforce and increase access to culturally appropriate care in our state's underserved regions."

Hernandez has been leading similar local initiatives for years, but CMSP will help expand and cement these efforts across the state. Through the program, pre-med community college students will undergo academic and professional development to help them transfer to a four-year university and then apply to medical school. Support will include focused mentoring, opportunities to network with potential clinical and research advisors, and guidance in applying for financial scholarships.

Thanks to the ongoing work of Hernandez and his team, UC San Diego School of Medicine was selected to lead one of the four regional hubs of the CMSP. UC San Diego faculty will serve as mentors to students from San Diego and Imperial counties, and CMSP students will later be admitted to the medical school.

"We are so excited to welcome our first cohort of community college students to the program, and look forward to seeing many of them join our medical school and PRIME programs in the coming years," Hernandez said.

Branching out

MARSHALL HAS SINCE GRADUATED FROM UC San Diego School of Medicine and is now a psychiatry resident at UCLA. Shaped by his experiences in PRIME-HEq, he is working to improve mental health care in the LGBTQ community. Looking back, Marshall sees the growth of these medical education programs as a testament to the hard work of students and faculty who have long appreciated this holistic approach to health care. Looking forward, he hopes the recognition from administrative and legislative leaders will help spread the mission of health equity even further.

"It's important to support underrepresented students as they study and serve these diverse communities, but they're not the only ones who will engage with the social determinants of health during their medical careers," Marshall said. "Every medical student should be prepared to understand and serve patients who face structural discrimination from the healthcare system."

Marshall envisions a future in which students in these programs can increasingly focus on community outreach and policy work, while courses on health disparities are reoriented towards the general medical school class. He also suggests the responsibility to engage in advocacy be shared among all students, and he is so far encouraged by the progress in this direction.

During his time at UC San Diego, Marshall helped design an introductory course in health equity that all incoming classes now complete during their orientation. Other new coursework and clinic programs in health disparities are increasingly attended by non-PRIME students. In fact, the growing community of medical students interested in incorporating these topics into their training has received an informal name: "PRIME Plus."

These shifts are just some of the many ways that Marshall, his peers, and their faculty mentors continue to shape medical education and care in San Diego and beyond.

"These programs have tangible effects on equity and diversity in health care," said Marshall, "and I'm glad to be part of an institution that cares enough about these causes to fund them." ●

The Student-Run Free Clinic Project Celebrates 25 Years

Since its inception in 1997, the UC San Diego Student-Run Free Clinic Project has provided respectful, empowering, high-quality health care to San Diego's underserved communities, all while inspiring the next generation of health professionals.

A staple of medical education at UC San Diego, the free clinic provides students with hands-on experience caring for patients from diverse cultural and socioeconomic backgrounds. Operating multiple nights a week at locations across the county, the clinics offer a variety of specialty services, including but not limited to cardiology, dermatology, ophthalmology, psychiatry, dentistry, nutrition, acupuncture and social services.

"The clinic is such an empowering place for medical students and really gives us the chance to make a meaningful difference in patients lives," said recent School of Medicine and PRIME-HEq alumnus Austin Marshall, MD, MPH, who previously served as the clinic's Psychiatry Clinic manager. In this role, he helped coordinate Spanish-speaking counseling groups and organized a psychiatrist panel on mental health care in underserved communities. Marshall calls UC San Diego's free clinic system "one of the best in the country."

LEADERSHIP

Ellen Beck, MD
Founding Director

Michelle Johnson, MD
Director

Natalie Rodriguez, MD
Associate Director

LOCATIONS
- Pacific Beach
- Downtown San Diego
- Lemon Grove
- Normal Heights
- Veterans Village of San Diego

ANNUAL SERVICES
Medical visits: 4,000+
Dental visits: 750+
Free prescriptions: 32,000+
Hours of psychotherapy: 570+
COVID-19 vaccinations: 500+

↓ **UC San Diego medical students help clinical teams provide quality care to underserved communities through the Student-Run Free Clinic Project.**

STOPPING CANCER BEFORE IT'S CANCER

BY COREY LEVITAN

CANCER CELL IMAGES COURTESY OF THOMAS DEERINCK, NCMIR, UC SAN DIEGO

Pre-Cancer Genome Atlas seeks telltale predictors of disease to come.

GENOMIC SLEUTHING BEHIND THE LATEST CANCER treatments is reaching for an even loftier goal: preventing cancer altogether.

The Pre-Cancer Genome Atlas (PCGA), led by scientist-physicians at Moores Cancer Center at UC San Diego Health, a National Cancer Institute-designated Comprehensive Cancer Center, has begun analyzing pre-cancerous tissues, such as abnormal cells, surrounding healthy tissue and immune cells, to develop predictive models of exactly how, when and why normal cells turn malignant, and to design preventive and therapeutic interventions.

Working with data from solid tumor and blood pre-cancer cells resulting from conditions and gene changes that increase cancer risk, the PCGA is seeking a new, more precise definition for pre-cancer based on consistent, systematic criteria.

"No one has actually studied pre-cancerous lesions at this genomic depth and scale to learn what makes them tick," said **Scott Lippman, MD**, Distinguished Professor of Medicine, associate vice chancellor for cancer research and care and PCGA co-director. "The PCGA is not only elucidating the elusive, tissue-specific biology underlying pre-cancerous lesions, it is redefining the field."

So far, the PCGA has obtained from UC San Diego and participating investigators around the globe a dataset of nearly 2,000 pre-cancer samples with matched-normal samples from 31 distinct pre-cancer types, with raw whole sequenced genomes (WGS) or exomes (WES). Exomes are the part of the genome consisting of exons that encode information for protein synthesis data. The estimated current size of the PCGA is 1.2 petabytes, the rough equivalent of 600 billion pages of standard printed text. The dataset is expected to grow exponentially as more samples and pre-cancer types are added.

The PCGA emerged from a Lippman-chaired 2017 National Institutes of Health (NIH) think-tank meeting in Bethesda, Maryland that included 25 global leaders in the field, including **Ludmil Alexandrov, PhD**, associate professor of cellular and molecular medicine at UC San Diego School of Medicine and co-director of the PCGA.

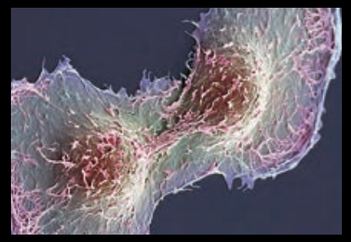
"The central idea was to replicate in pre-cancer the success of the NIH's 2006 Cancer Genome Atlas (TCGA) program," Alexandrov said. (The TCGA has collected paired tumor and normal tissue sets from 11,000 patients across 33 tumor types with aligned WGS or WES data.)

Main challenge

DEVELOPING A FIXED, cross-sectional, tissue-site definition of a biological entity with time, space and intervention variables isn't easy. It was easier to define pre-cancer 30 years ago when, Lippman noted, "we knew so little about pre-cancer biology that there was little debate over what it was or, more accurately, what we thought it was."

By definition, cancer is a genetic disease with more than 200 molecular types characterized by somatic mutations or recurrent (or frequent) somatic copy-number alterations — abnormalities that result in the loss or gain of a copy of a chromosome arm or region and lead to chromosomal instability.

This often results in the translocation, duplication or deletion of entire chromosomal regions or whole chromosomes themselves. This is known as aneuploidy: the presence of an abnormal number of chromosomes and arms in the genome. It's very rare in healthy tissues, but frequently found in cancer. Aneuploidy and other genomic events can cause normal cells to become abnormal, unregulated precancerous cells.



↑ HeLa cell division.

While experts largely agree on what is a cancer, (for example, what to include in the TCGA), pre-cancer definitions are less clear and relatively fluid, even among experts regarding a specific lesion type and tissue site.

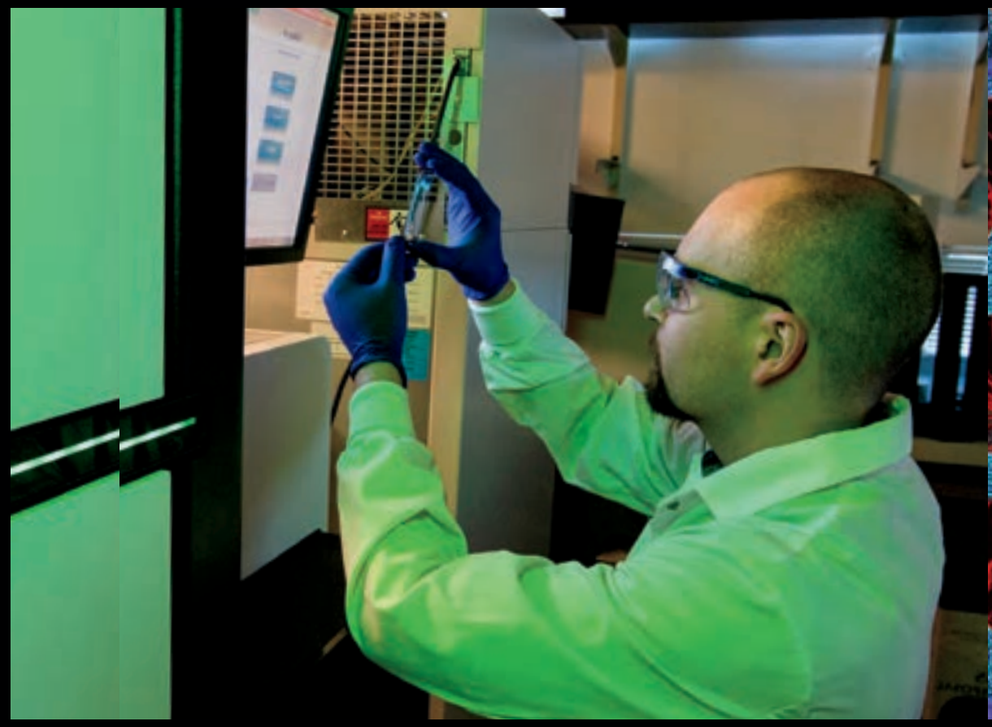
Moreover, pivotal advances in DNA sequencing technology, data science and computational biology have actually added to the difficulty of definition. In recent years, for example, researchers at Massachusetts Institute of Technology, Dana Farber Cancer Institute and Sanger Institute have found that most "healthy" people harbor some mutations in normal epithelial cells that have previously been associated with cancer.

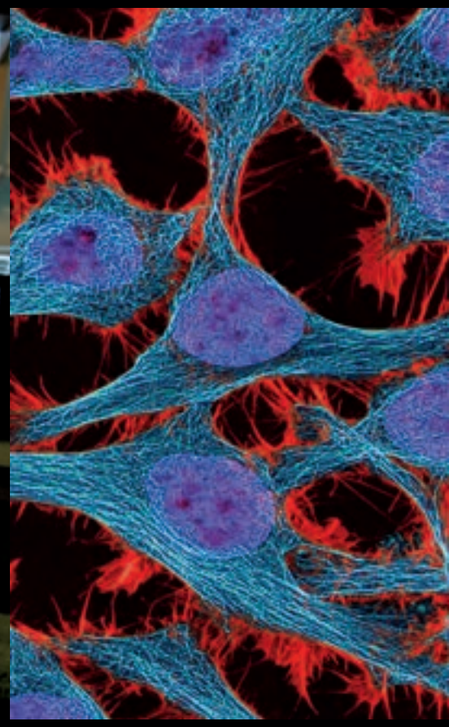
"So, context is everything when it comes to somatic clonal evolution in normal tissue," said Lippman. "For example, there are benign growths that never invade nearby tissue or spread but also share the same cancer driver mutations found in malignant lesions.

"If you define pre-cancer by genetic abnormalities, we all are carrying the same type of abnormal cells we see in cancer. The million-dollar question becomes 'What makes only some mutated cells become cancerous?'"

"If you define pre-cancer by genetic abnormalities, we all are carrying the same type of abnormal cells we see in cancer. The million-dollar question becomes 'What makes only some mutated cells become cancerous?"

SCOTT LIPPMAN, MD





Early answers

PCGA TEAM MEMBERS SAY THEY ARE FINDING answers. Some involve the APOBEC3 family of enzymes, part of the internal immune response to restrict viruses from entering the cell. In blood, for example, one member of the APOBEC3 family has been implicated in myeloproliferative neoplasms, a group of premalignant conditions in which blood cells grow abnormally in the bone marrow.

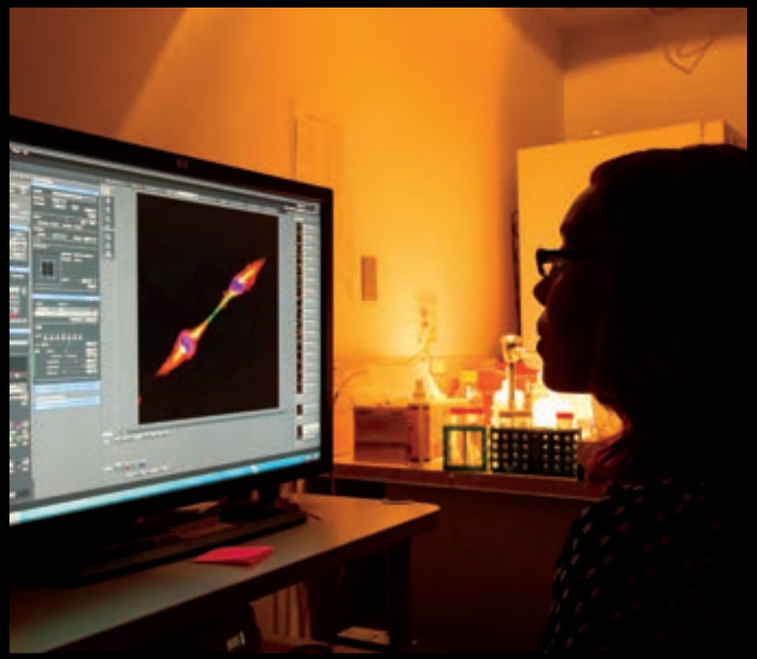
"When APOBEC3C deaminase is activated in stem cells for a long period of time, it tells that cell, 'You're under attack by a retrovirus or some sort of viral pathogen, so you'd better clone yourself,'" said **Catriona Jamieson, MD, PhD**, professor of medicine, deputy director of Moores Cancer Center and a PCGA co-investigator.

"And that's what's uniquely malignant about APOBEC3C. It's actually mutating a genome, and now you have a mutated stem cell that just cloned itself."

Progress is also being made by PCGA researcher **Jason Sicklick, MD**, professor of surgery at UC San Diego School of Medicine and a leader in the study of mutational drivers for rare gastrointestinal stroma tumors (GISTs). Sicklick is currently investigating a previously under-recognized and rarely studied GIST precursor lesion thought to arise from cells of fibroblastic and/or smooth muscle origin within the stomach wall.

"Our recent transcriptomic pathway analysis at the single-cell level is getting close to elucidating the elusive stromal cell of origin of these mysterious lesions," Sicklick said.

By further understanding the cellular origin and progression of these lesions, Lippman said Sicklick's group is helping to prove the power of PCGA to "uncover important genomic events that both redefine the pre-cancer landscape and can drive therapeutic and early detection research in ways never realized before."



Hide and seek

A KEY UNANSWERED QUESTION IN TUMOR BIOLOgy is how a pre-cancerous cell escapes the immune system, evolving from so-called "immune hot" to "immune cold." (Hot tumors are typically recognized by cytotoxic immune cells and likely to provoke a strong immune response, while cold tumors are often impenetrable by immune cells.)

For some head and neck cancers, the answer lies on the short "p" arm of chromosome 9, according to PCGA research. Reported last year in *PNAS*, Alexandrov, Lippman and colleagues identified the genomic switch that triggers the invasive-disease and immune hot-to-cold transition in precursors of human papilloma virus-negative head and neck squamous cell carcinoma, the most common and lethal subtype of this cancer. (See sidebar.)

"In pre-cancer, loss of a region of 9p, 9p21 triggers an immune-hot response, keeping the pre-invasive lesion in check, preventing pre-cancer cells from invading through the epithelial basement membrane," said Lippman. "But as the lesion evolves, the size of the chromosome 9p21 deletion expands, until the entire arm is lost. Gene dissection studies remarkably revealed that the 9p arm is a hotbed of immune-regulatory genes."

"It's this progressive loss of immune-regulatory genes on the chromosome 9p arm that drives pre-cancerous cells to acquire properties to evade immune surveillance and invade through the basement membrane, causing profound depletion of cytotoxic T- cells in the immune microenvironment surrounding the tumor," said Alexandrov. "This, in turn, drives cancer cells to spread, recur and resist immunotherapy."

These 9p-deletion results were confirmed and are now used by oncologists as a biomarker test to help them decide whether a patient with HNSC should receive potentially curative immune-checkpoint inhibitors, a type of immunotherapy that uses antibodies to make tumor cells visible to a patient's immune system.

"Identifying the genomic switch which triggers the precancer invasive-disease transition establishes the PCGA as a vital tool for oncologic research," said Lippman. "It provides a new paradigm for probing other pre-cancer sites to drive much-needed prevention, early detection and therapeutic research strategies."

Another way pre-cancers escape our immune response is by disguising their mutations.

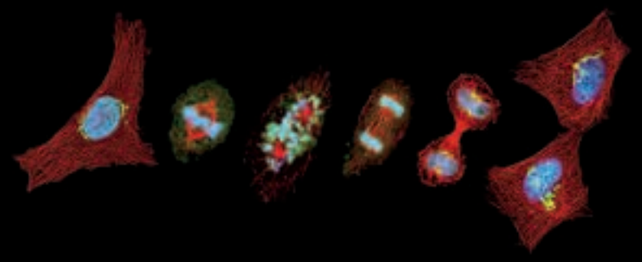
"There are many ways pre-cancers do this," said **Silvio Gutkind, PhD**, chair of the Department of Pharmacology and a PCGA co-investigator. "One is by not exposing their antigens, so T cells will never see all these mutations. Another approach is to have inflammatory cells release cytokines and prostaglandins, which throw up a shield that says, 'Don't come here. We are cool. Don't worry about us.'"

Gutkind equates spotting the telltale signs that a healthy cell is becoming pre-cancerous to catching a thief based on fingerprints. "The organs in which they arise may be different, but the fingerprints of a carcinogen are the same. And they help you to start seeing some order in the constellation of possibilities."

The ambitions and expectations of PCGA researchers aren't necessarily to eventually prevent every cancer from happening, but to drastically diminish frequency and consequences.

"A better way of thinking about our goal," said Gutkind, "is to make cancer a chronic disease that's manageable and that you don't need to die from, like how HIV, diabetes or hepatitis C have become.

"It's not rocket science. It's just an issue of identifying and then targeting what makes a cell vulnerable to this transition from pre-cancer to cancer." ●



HEAD START

HEAD AND NECK squamous cell carcinoma (HNSC), which develops in the mucous membranes of the mouth, nose and throat, is the sixth most common cancer worldwide, with case numbers rising.

If detected early, most HNSC cases are treatable, even curable. The rub is that most cases are not caught early, resulting in poorer five-year relative survival rates (the percentage of patients who are alive five years after diagnosis and treatment). Cancer survival rates are highly variable, dependent upon multiple factors in each patient, but the rate is notoriously poor for patients with HPV-HNSC, with a median of five to six months in recurrent or metastatic disease.

"We don't have very good screening mechanisms, so we can't see most head and neck cancers until they're big," said **Joseph Califano, MD**, director of the Gleiberman Head and Neck Cancer Center at UC San Diego Health. "HPV-related oropharynx cancer has become an epidemic in this country, with incidence rates continuing to rise, but we can't catch it early just by looking in the back of the throat because there aren't specific symptoms of early disease."

(Califano's lab is developing novel devices and technologies to detect integrated viral DNA and epigenetic markers of early HPV-related disease.)

Insights gleaned from PCGA studies of HPV-negative HNSC precursor lesions are informing future efforts to develop preventive and individually tailored treatments for patients determined to be at higher risk of developing HPV-related cancer, such as those with long-term oral HPV infections, which have no known precursor lesions.

For HPV-negative HNSC, where pre-cancerous lesions are well established, the PCGA already offers hope. Califano cited the 2021 report of the first clinical trial conducted by Lippman and Gutkind using PCGA data that found that the diabetes drug metformin reduced histological progression of oral premalignant lesions — the most common precursor of the most common and lethal head and neck cancer type.

"It seems like such a simple concept: instead of waiting for cancer to develop, intervene and they never even develop it," Califano said. "You don't have to debilitate people with very large surgeries, radiation therapy or chemotherapy."

PRECISION MEDITATION

BY NICOLE MLYNARYK

Backed by neuroscience and individually customized, mindfulness meditation enters an era of clinical precision.

GOT A PROBLEM? WE (MAY SOON) HAVE A MEDI-tation for that. Mindfulness meditation is among the fastest-growing trends in health care and wellness. A quick perusal of any popular meditation app reveals the variety of conditions it can purportedly treat, including stress, anxiety, depression, pain, insomnia and loneliness.

But can any single meditation practice really serve them all?

Researchers at the UC San Diego T. Denny Sanford Institute for Empathy and Compassion are paving the way for a modern era of targeted mindfulness-based interventions. Through a series of studies, interdisciplinary teams are breaking down mindfulness into distinct components and assessing what kinds of symptoms each component is most effective at treating.

Their goal is to develop evidence-based mindfulness techniques tailored to different patient populations: A student struggling to focus in class. A lonely senior experiencing depression. A patient suffering from chronic back pain. Each would be prescribed a unique treatment plan featuring customized meditations.

"We're getting so sophisticated about precision medicine when it comes to drugs and surgeries; it's now time we invest the same level of precision into cognitive training," said **Fadel Zeidan, PhD**, associate professor of anesthesiology at UC San Diego School of Medicine.

Zeidan and colleagues are using the latest tools in neuroscience and psychology to study the effects of mindfulness meditation on the brain and behavior. At its core, mindfulness is centered on the act of bringing one's attention to the present moment, without making any judgements in the process. The technique evolved from traditional Eastern practices originating thousands of years ago, but can now be evaluated through the scientific method.

"We ultimately want to be able to prescribe personalized mindfulness programs tailored to what each person needs help with — not just based on what we think will work, but on what actually works according to the data," Zeidan said.

The case for customization

ANOTHER MEMBER OF THE SANFORD TEAM is **Ariel Lang, PhD**, a licensed clinical psychologist and professor of psychiatry at UC San Diego School of Medicine and Herbert Wertheim School of Public Health and Human Longevity Science. As director of the Center of Excellence for Stress and Mental Health at the VA San Diego Healthcare System, Lang has long studied the benefits of meditation in treating military veterans with post-traumatic stress disorder (PTSD). The evidence so far suggests mindfulness does help relieve certain PTSD symptoms, but according to Lang, the effects are modest for many veterans.

"Everyone's needs are slightly different," Lang said. "For those particularly struggling with anxiety or irritability, mindfulness meditation can be a helpful tool to calm their nervous systems. But PTSD has many other layers to it, so we wondered if mindfulness might be more effective if we added a specific contemplation tailored to these other needs."

Veterans with PTSD commonly struggle to relate to others after military service, particularly civilians who may not understand what deployment entails. The resulting social isolation can exacerbate feelings of depression and anxiety. To address this issue head on, Lang's lab began training veterans in compassion meditation, a form of meditation specifically designed to strengthen and sustain compassion towards others.

In the 90-minute sessions, trainees were guided to tap into a sense of common humanity, contemplating the life experiences and goals we all share. The theory is that by fostering these traits of empathy and compassion, the veterans might feel a greater ease in relating to others, which might slowly restore their sense of belonging.

After 10 weeks of practice, the participants reported greater social connectedness, elevated mood and reduced symptoms of depression. Importantly, a control group that completed a general relaxation training instead of compassion meditation did not show these same improvements.

But if isolation was the problem, why not focus on providing more social resources? Lang is an advocate for social support groups, but asserts that compassion meditation remains an important addition to PTSD treatment plans.

"If you just ask people to go socialize, you're not addressing the guilt, shame, irritability or anxiety that was holding them back in the first place," said Lang. "Our best chance at helping folks reconnect with others is to first address the feelings and beliefs that were getting in the way."

With compassion meditation showing promising results in veterans, Lang and her team are now testing its effectiveness in other populations experiencing social isolation, including seniors and individuals with chronic pain.

"It's likely that different meditative practices are going to get at different aspects of psychopathology," said Lang. Studies like this, she said, help scientists optimize the techniques and prepare them to be successfully administered in clinical settings.

"Many people already support the use of mindfulness meditation to enhance well-being. But when you talk to a therapist, they have to first suggest the most evidence-based approaches. So that's what we're doing — finally getting that evidence."

↑ **Fadel Zeidan, PhD**

↑ **William Mobley, MD, PhD**

This framework has inspired another major research effort at the institute in which Zeidan and colleagues plan to dissect the meditative technique even further.

In the new study, participants are split into different meditation groups, each focused on a particular component of meditation practice. One group is trained to non-reactively focus on their breath, while another focuses on their body using the "body scan" technique. A third group is trained to cultivate compassion towards others, while a fourth cultivates compassion toward themselves. The mindfulness groups are compared to two control groups, one of which learns a form of non-mindfulness meditation focused on deep breathing

and the other spends sessions listening to an audio book, not meditating at all.

The study is ongoing, but preliminary results suggest that after just four days of training, each group experiences distinct behavioral effects, particularly regarding anxiety and social connectedness.

"By disentangling the many dimensions of mindfulness, we'll be able to see how each component of the meditative experience uniquely targets health," Zeidan said. "Then we can start combining effective dimensions into customized programs depending on the individual's needs."

Health care workers and caregivers, for example, may show high levels of compassion for others but could benefit from developing more compassion for themselves. For individuals with neurological disorders, such as multiple sclerosis, some forms of mindfulness may be quite mentally fatiguing, "but if something less cognitively demanding like deep breathing is helpful, then that's what we want to prescribe in that particular scenario," Zeidan said.

"We're getting so sophisticated about precision medicine when it comes to drugs and surgeries; it's now time we invest the same level of precision into cognitive training."

FADEL ZEIDAN, PHD

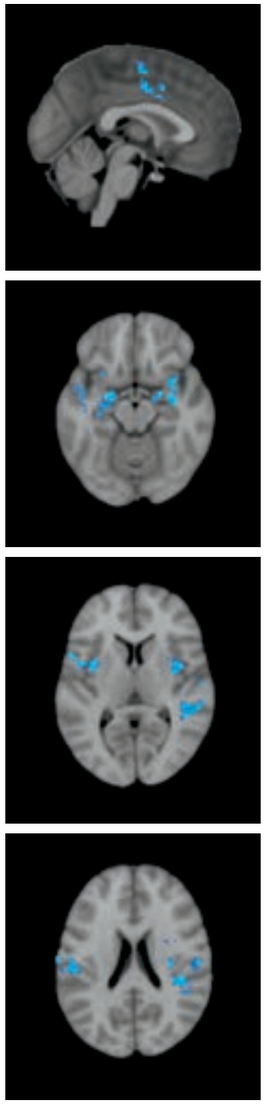
"If we want to make this a real science, we have to remove our biases and expectations. If mindfulness doesn't work, we're not going to use mindfulness. And when it does work, we're not suggesting it's the end-all be-all. Multimodal problems require multimodal solutions, and we want to know when mindfulness can be a part of that."

Your brain on mindfulness

TO ZEIDAN AND OTHER RESEARCHERS AT THE Sanford Institute, mindfulness cannot be fully understood without explaining what it does to the brain.

"Neuroscientists have historically struggled to receive funding for studies examining the effects and biological substrates of empathy and compassion, but through the founding of this institute, UC San Diego is now uniquely poised to pioneer this new field," said Zeidan.

In a growing line of research, Sanford scientists are exploring what features of the brain support mindfulness, compassion and empathy. The findings will help explain how these traits grow and diminish across individuals and disease states. They'll also be a useful biomarker to evaluate the success of different mindfulness techniques, and determine effective treatment doses, such as the length and frequency of meditation sessions necessary to see a real effect.



↑ **UC San Diego scientists are using neuroimaging tools to learn how meditation affects the brain. Here, the Zeidan lab showed that individuals who meditated while receiving a painful stimulus showed reduced activity (blue) in many brain areas involved in pain perception.**

"Many meditation programs involve a lot of discussion about empathy and compassion, but findings from our laboratory and others' demonstrate that it really comes down to mental training," Zeidan said. "You can't just lecture someone into becoming more empathetic — enhancing compassion requires unique cognitive training approaches, and we can now see this process being reflected by reliable changes in the brain."

To observe these brain changes, the Zeidan lab measures participants' neural activity before and after mindfulness training using functional magnetic resonance imaging (fMRI). Such fMRI studies have started to explain how mindfulness works, particularly in reducing anxiety.

It's now known that meditation can increase activity in the prefrontal cortex (PFC), a brain region associated with cognitive control and executive functioning. Anyone who's experienced a state of high anxiety can attest that it's not the best time to rely on one's executive functions (such as attention, decision making and impulse control). So bringing these back online through enhanced prefrontal activity seems to have a positive effect. Furthermore, the PFC plays an important role in regulating the amygdala, a brain area involved in processing emotions and fear. Thus, by increasing PFC activity, mindfulness also reduces amygdala activity, and anxiety is quelled.

In another recent study, Zeidan's lab looked at the effects of mindfulness meditation in treating pain. Participants completed several 20-minute training sessions during which they were instructed to notice their thoughts, sensations and emotions without judging or reacting to them. Participants' brains were later scanned while they experienced a painful heat stimulus. Those who were actively meditating during the stimulus reported significantly lower pain intensity and unpleasantness.

When the researchers looked at the participants' brain activity, they found that pain relief was associated with reduced synchronization between the thalamus, a brain region that relays incoming sensory information to the rest of the brain, and parts of the default mode network that mediate self-awareness and appraisal. The more these areas were decoupled or deactivated, the more pain relief the participant reported. So while pain signals still entered the brain, they did not seem to be as closely integrated with the individuals' sense of self.

"One of the central tenets of mindfulness is the principle that you are not your experiences, and we're now finally seeing how this plays out in the brain during the experience of acute pain," said Zeidan.

"Fadel's work strengthens our ability to understand the interface between the brain and mind, and use this new knowledge to enhance both science and meditative practice," said institute director **William Mobley, MD, PhD**, Distinguished Professor of Neurosciences at UC San Diego School of Medicine. "This kind of research will allow us to increasingly bridge from practice to brain function and back again, and the result will be much more rigorous and evidence-based support for mindfulness."

This isn't to say that anyone interested in the health-promoting benefits of meditation needs to have their brain scanned to ensure it's working. But as with the development and testing of any new therapeutic, the more thoroughly scientists can evaluate its mechanism up front, the more successful the treatment is likely to be.

"We want mindfulness training to be as efficient and effective for our patients as possible," said Zeidan. "But it's clear you don't have to be a monk to reap the benefits of mindfulness, and while we work to optimize the techniques, there's likely no harm in practicing the ones we currently have."

So as we wait for the future of precision mindfulness, scientists encourage us to continue embracing the present. ●

↑ **Ariel Lang, PhD, (second from right) and her lab practice mindfulness meditation at the "Stonehenge" art installation on campus.**

THE CAMPAIGN FOR UC SAN DIEGO

Launched in 2012, the Campaign for UC San Diego was originally intended to fundraise $2 billion, an audacious goal at a time when the university's endowment was a comparatively modest $555 million. Harvard, by comparison, has an endowment in excess of $41 billion.

62 years

At just 62 years old, UC San Diego became the youngest university in the country to reach a multibillion-dollar campaign goal. Harvard is 387 years old.

454 areas of campus

Campaign funds provide support to 454 different areas of campus and include $100 million given by Joan and Irwin Jacobs to help build the Jacobs Medical Center at UC San Diego Health, which opened in 2016; $200 million donated by T. Denny Sanford to support stem cell research and create an eponymous institute to study and promote empathy and compassion; and $375 million dedicated to student support and more than 300 new scholarship funds, such as the Chancellor's Associates Scholars Program, which provides scholarships and academic resources to students from underserved populations.

$7B

Approximately $7 billion has been invested in teaching space, labs, medical facilities and student housing. Enrollment now stands at roughly 42,000 students. By Fall 2025, half of that total will be offered on-campus housing. UC San Diego is the second most applied to institution in the country (after UCLA), with more than 100,000 applications annually, according to U.S. News & World Report.

$3.05B

When the Campaign officially ended in July 2022, $3.05 billion had been raised from more than 164,000 individuals, foundations and corporations. The vast majority of donations (91 percent) were less than $1,000 each, but almost 400 donors gave $1 million or more in support. More than 46,600 alumni donors contributed $257.2 million, and nearly 14,000 students donated. The university endowment now exceeds $2.58 billion, a 365 percent increase.

TEN

The past 10 years have also marked a period of extraordinary growth under the leadership of Chancellor Pradeep K. Khosla. UC San Diego has become a global research and academic medical powerhouse, with more than $6.9 billion (FY22) in annual revenues (a 103 percent increase from 2012) and $1.64 billion (FY22) in sponsored research (62 percent). Inpatient care at UC San Diego Health has increased 44 percent, from 554 patient beds to 799.

$1.48B

Nearly half of the Campaign total ($1.48 billion) comprised of donations designated for health sciences, including $50 million to the Viterbi Family Department of Ophthalmology and Viterbi Family Vision Research Center; $50 million to create the Eptein Family Alzheimer's Research Collaboration with the University of Southern California; and $25 million to establish the Herbert Wertheim School of Public Health and Human Longevity Science.

PICTURES OF HEALTH

From La Jolla to Hillcrest, across its missions of education, research and clinical care, the past dozen years or so have been a period of extraordinary growth at UC San Diego Health, the regions' only academic medical center.

LA JOLLA CAMPUS

↑

JACOBS MEDICAL CENTER

2016 / $943M / 509,500 SF

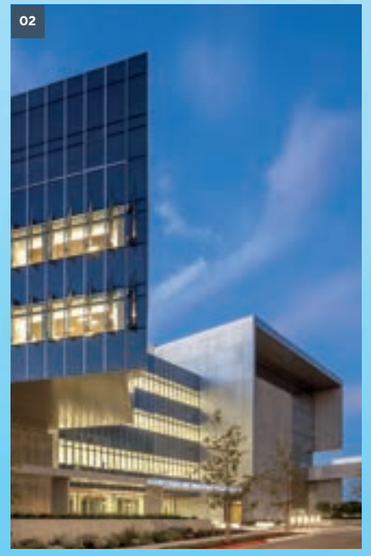
The 10-story complex, named in recognition of Joan and Irwin Jacobs, includes three specialty pavilions for advanced surgery, cancer care and women and infants. The 363-bed site incorporates the earlier 119-bed Thornton Hospital and Perlman Ambulatory Care Center.

→

SHILEY EYE INSTITUTE

1991 / $8M / 90,000 SF

Built with support from Donald and Darlene Shiley, the three-story structure houses the Viterbi Family Department of Ophthalmology, the Hamilton Glaucoma Center, the Jacobs Retina Center and the Ratner Children's Eye Center. The facility has undergone several expansions, with another underway to add clinical space and support facilities.



←

ALTMAN CLINICAL AND TRANSLATIONAL RESEARCH INSTITUTE

2016 / $269M / 359,000 SF

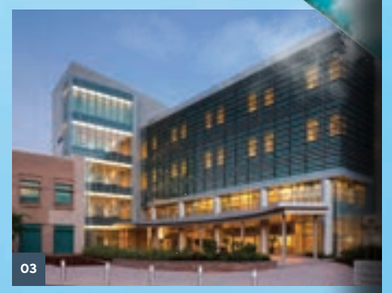
Launched with a gift from Steve and Lisa Altman, ACTRI literally connects basic research with clinical care: a bridge links the seven-story structure to Jacobs Medical Center. ACTRI provides infrastructure and support for basic, translational and clinical research.

→

SULPIZIO FAMILY CARDIOVASCULAR CENTER

2011 / $136M / 128,000 SF

Sulpizio is the region's first academic-based facility to combine all heart and vascular-related services, programs and technology under one roof. Development began with a gift from Richard and Maria Sulpizio.



HILLCREST CAMPUS

In 1966, UC San Diego took over operations of the county hospital in Hillcrest. In 1981, the university purchased the hospital outright. Over the years, UC San Diego Medical Center in Hillcrest has been upgraded, expanded and adapted to changing needs, but seismic safety mandates require that much of the site be replaced before 2030.

OVER THE NEXT 14 YEARS, THE $2.5-$3 BILLION DEVELOPMENT PLAN WILL TRANSFORM 62 ACRES INTO FIVE DISTRICTS IN FIVE PHASES:

PHASE 1

The 19-acre health care district launches with a 251,000-square-foot outpatient pavilion, plus a 1,850-space parking structure. Projected completion for the outpatient pavilion is 2025; the parking structure is slated to open in late 2023.

PHASE 2

A 9-acre residential district will include 500 housing units in multistory towers providing long-term patient and family housing. Structures will also include parking, retail space and developed open space such as parks and plazas.

PHASE 3

A multipurpose facility will house research laboratories, administrative space and additional parking.

PHASE 4

A 1.4 million-square-foot, 300-bed hospital tower will replace the current 390-bed facility, with associated medical offices, research and support space. The existing hospital will be subsequently demolished.

PHASE 5

A 2-acre mixed-use district will include fitness/wellness facilities, retail space and medical offices. Additional residential towers with 500 units front a 4-acre open space featuring publicly accessible parks, plazas and pathways, as well as spaces for entertainment and educational events.

PRESERVED LAND

The canyon district comprises roughly 28 acres of largely undisturbed natural open space with limited public access to preserve natural habitats and local animal and plant species.

LA JOLLA CAMPUS

JACOBS MEDICAL CENTER
2016 / $943M / 509,500 SF

The 10-story complex, named in recognition of Joan and Irwin Jacobs, includes three specialty pavilions for advanced surgery, cancer care and women and infants. The 363-bed site incorporates the earlier 119-bed Thornton Hospital and Perlman Ambulatory Care Center.

ALTMAN CLINICAL AND TRANSLATIONAL RESEARCH INSTITUTE
2016 / $269M / 359,000 SF

Launched with a gift from Steve and Lisa Altman, ACTRI literally connects basic research with clinical care: a bridge links the seven-story structure to Jacobs Medical Center. ACTRI provides infrastructure and support for basic, translational and clinical research.

SULPIZIO FAMILY CARDIOVASCULAR CENTER
2011 / $136M / 128,000 SF

Sulpizio is the region's first academic-based facility to combine all heart and vascular-related services, programs and technology under one roof. Development began with a gift from Richard and Maria Sulpizio.

SHILEY EYE INSTITUTE
1991 / $8M / 90,000 SF

Built with support from Donald and Darlene Shiley, the three-story structure houses the Viterbi Family Department of Ophthalmology, the Hamilton Glaucoma Center, the Jacobs Retina Center and the Ratner Children's Eye Center. The facility has undergone several expansions, with another underway to add clinical space and support facilities.

LA JOLLA INSTITUTE FOR IMMUNOLOGY
2006 / 145,000 SF

Founded by a coalition of academia and industry, with close ties to UC San Diego, to conduct basic research of diseases of the immune system. Located within UC San Diego's Science Research Park, LJI is an independent, nonprofit research institute, but shares resources and faculty appointments with UC San Diego.

CENTER FOR NOVEL THERAPEUTICS
2019 / $92M / 137,500 SF

A collaboration between academic research and private industry, CTN is a shared drug discovery incubator for scientists from UC San Diego Moores Cancer Center, Kyoto University and biotechnology companies.

MOORES CANCER CENTER
2005 / $75M / 274,000 SF

Built with support from Rebecca and John Moores, the multidisciplinary facility brings together research laboratories, outpatient clinical care and cancer support services. The National Cancer Institute-designated center runs numerous clinical trials for novel and personalized cancer treatments.

KOMAN FAMILY OUTPATIENT PAVILION
2018 / $1.3B / 156,000 SF

The outpatient pavilion includes eight surgery suites, basic and advanced imaging, physical therapy and pain management plus infusion and apheresis services. Named in honor of Bill and Amy Koman and family.

IN THE YEARS TO COME

RESEARCH

09

The Viterbi Family Vision Research Center will house interdisciplinary ophthalmological research, with a focus on glaucoma, retina degeneration and restoring vision loss. Construction of the five-story, 100,000-square-foot building is slated to begin in early 2023.

10

A "clinical research village" aims to integrate clinical and research facilities supporting interdisciplinary patient care. A series of structures housing laboratory space will anchor Campus Point Drive and facilitate further collaboration between clinical and research faculty.

CLINICAL

11

An expansion of Moores Cancer Center.

12

A new inpatient clinical tower adjacent to Jacobs Medical Center, with a potential focus on cardiovascular care.

13

An additional outpatient pavilion adjacent to Jacobs Medical Center.

14

An additional outpatient or clinical care facility, with a potential focus on mental health services.

RESIDENTIAL

15

A mixed-use complex has been proposed to include a 35,000-square-foot conference center, a 300-room extended-stay hotel for UC San Diego Health patients and families, and additional residential housing. The complex could also house related spaces, such as a spa, a fitness center, therapy areas and dining options.

P

Multistory parking structure

*With the exception of the Viterbi Family Vision Research Center, which received final UC Regents' approval in November 2022, the described projects are proposed and must still undergo requisite design, planning, financing and approvals.

BY THE NUMBERS

Awards · Facilities · Staff · Procedures

No.1
Ranking of UC San Diego Health by U.S. News and World Report in San Diego

5th
Rank in California

SIXTY
Age of the current Hillcrest hospital, which replaced the first county hospital built at the site in 1904

47%
Percentage of current Hillcrest medical campus buildings constructed prior to 1970

799
Total licensed beds at UC San Diego Health

90%
Percentage of Hillcrest campus buildings that will be replaced

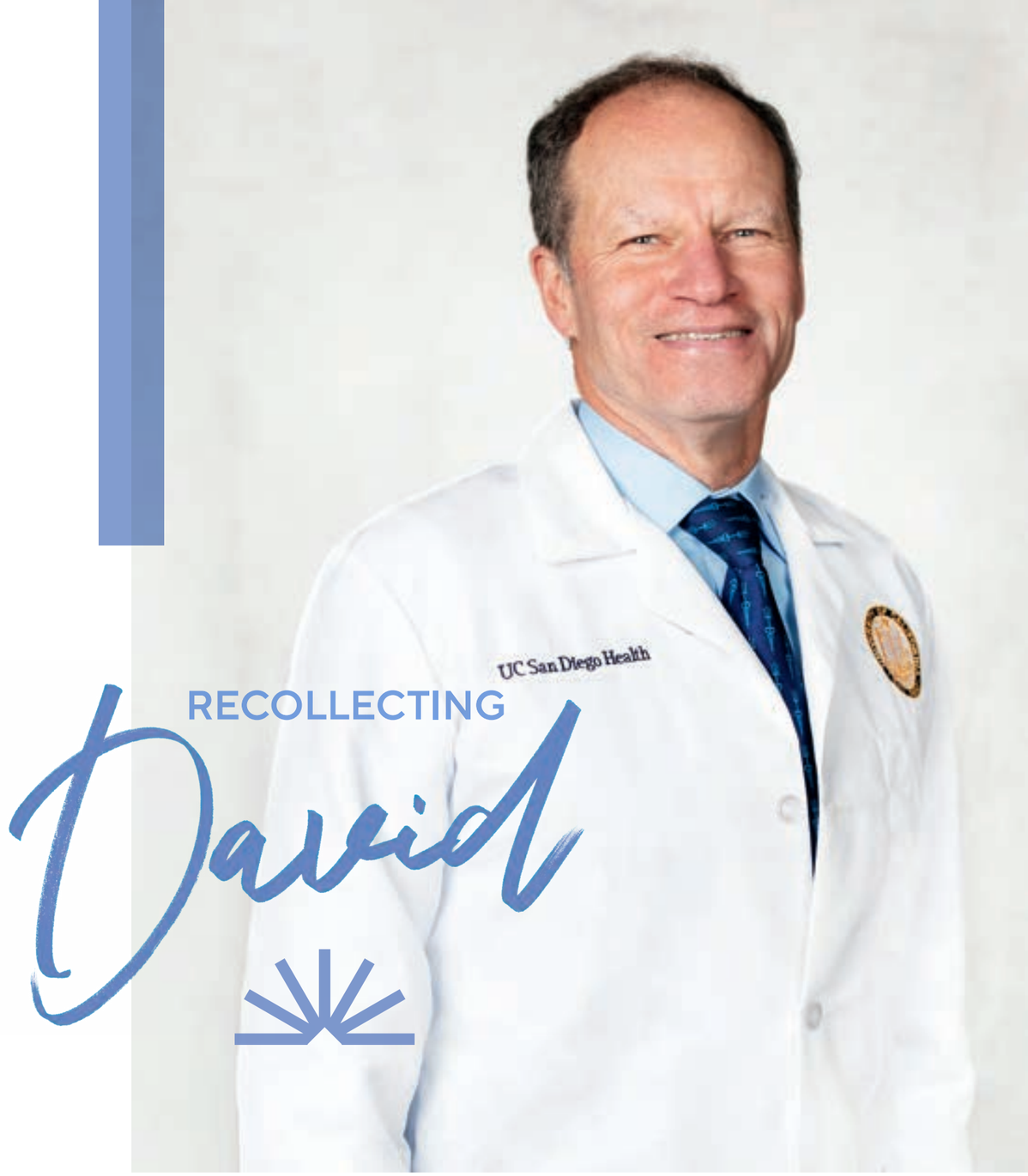
4,450
Current number of faculty and staff working at Hillcrest site

9K
Approximate total number of UC San Diego Health employees

5,200
Projected number of faculty and staff in Hillcrest in 2035

32.5K+
Annual hospital admissions at UC San Diego Health, both La Jolla and Hillcrest

1 Million
Approximate annual outpatient visits and surgeries



RECOLLECTING David

As vice chancellor and dean of the School of Medicine, David Brenner rewrote what Health Sciences was and could be at UC San Diego.

BY SCOTT LAFEE

DAVID A. BRENNER, MD, ALREADY HAD A HISTORY with the UC San Diego School of Medicine when he arrived in 2007 as its new dean and vice chancellor for health sciences. He had been a gastroenterology fellow at UC San Diego in 1985-86, and then a faculty member until 1993. So he knew what he was getting into, which was why he had sought the job.

"UC San Diego was — and is — the most collaborative institution I've ever known," said Brenner, who stepped down as vice chancellor July 1, 2022, and as dean in 2018. "Everywhere I had been was more siloed and limiting. But here, there was a sense of doing research that transcended boundaries. There was a feeling of doing really hard things, of being pushed in a good way.

"Everything was organized by shared interests, not by departments or labels, by smart people with aspirations. People talked to other people. Gastroenterologists like me didn't just speak to other gastroenterologists. Everybody was willing to try anything to further bigger goals. I remember as a gastroenterology fellow talking with Michael Karin about cancer, and working with him. All these years later, we're still collaborating."

As new dean and vice chancellor, Brenner wanted to nurture these evident strengths, but even more so, to expand them and embrace the combined missions of education, research and clinical care.

"We say it now with familiarity. It's our tripartite mission. But that wasn't necessarily the case in 2007," said Brenner. "There was a deep investment in research, but less of a connection between basic science and clinical excellence. The health system was smaller, and, in some ways, maybe seen only as a provider of patients to help teach medical students.

"People thought you couldn't really do all three things well: research, teaching and caring for patients. Faculty believed that the size of the pie was fixed. If you emphasized research, that meant smaller slices for other things. I thought we needed to make a bigger pie."

Above: David Brenner, MD, (far left), Sunny Smith, MD, and William Mobley, MD, PhD, meet with the Dalai Lama at his home in Dharamsala in 2019 to discuss the idea of creating a new institute to study empathy and compassion.
Right: Brenner with Cheryl A.M. Anderson, PhD, founding dean of the Herbert Wertheim School of Public Health and Human Longevity Science.

> "UC San Diego was — and is — the most collaborative institution I've ever known."
>
> DAVID BRENNER, MD

Then and now

AT THE TIME OF HIS HIRING, BRENNER ASSUMED oversight of the School of Medicine (founded in 1968), the five-year-old Skaggs School of Pharmacy and Pharmaceutical Sciences, the UC San Diego Medical Center in Hillcrest (once the site of the county hospital) and the UC San Diego Medical Group.

In 2007, these enterprises encompassed 900 physicians, pharmacists and scientists on faculty, 7,500 staff, approximately 600 medical and pharmacy students, and a health system that served roughly 125,000 patients annually.

The following 15 years under Brenner would be marked by extraordinary expansion and progress, so much so that the headline of a 2015 profile in *The San Diego Union-Tribune* proclaimed him "The Empire Builder."

With the opening of the Herbert Wertheim School of Public Health and Human Longevity Science in 2019, there are now three professional schools in Health Sciences and two health campuses in Hillcrest and in La Jolla, the latter of which includes Jacobs Medical Center, Sulpizio Cardiovascular Center, Moores Cancer Center, Shiley Eye Institute, Altman Clinical and Translational Research Institute (ACTRI) and Koman Family Outpatient Pavilion, plus primary care and same-day clinics throughout Southern California.

The School of Medicine now boasts almost 1,700 faculty in 19 departments, 967 residents and fellows, more than 530 MD students and 80 MD-PhD students. The Skaggs School of Pharmacy has 55 faculty members and more than 250 students, plus 30 drug discovery labs. The Wertheim School of Public Health has 80 faculty, nearly 700 students and more than 50 funded research groups.

The growth of UC San Diego Health has been even more dramatic: more than 10,000 employees, 808 licensed beds (up from less than 400 in 2007), nearly 1 million outpatient visits and surgeries annually, more than 31,000 hospital admissions each year and revenue of more than $2.6 billion (up from $643 million in 2007). In collaboration with ACTRI, the health system manages roughly 2,400 clinical trials each year, enrolling more than 7,000 patients in novel treatments often unavailable anywhere else.

U.S. News and World Report ranks UC San Diego Health #1 in San Diego and #5 in California, with 10 specialties judged in the top 50 nationally.

"David's vision and support have been vital to the health system's steady growth and achievement," said **Patty Maysent**, CEO of UC San Diego Health. "As the region's only academic medical center, we embrace the greatest challenges and responsibilities, from training new generations of doctors and developing the newest advances in patient care to providing essential leadership and infrastructure required by public health crises like the COVID-19 pandemic. David has always advocated for excellence."

Growth can be measured in new buildings, too. During Brenner's tenure, the Sulpizio Cardiovascular Center opened in 2011, the region's first academic-based facility to combine all heart and vascular-related services, programs and technologies under one roof; the T. Denny Sanford Medical Education and Telemedicine Building, also in 2011; the East Campus Office Building in 2012; the Biomedical Research Facility II building in 2014; the 10-story, 364-bed Jacobs Medical Center in 2016, featuring advanced care in surgery, cancer and labor and delivery; ACTRI, also in 2016; the Koman Outpatient Pavilion in 2018; and the Center for Novel Therapeutics in 2019.

In September 2021, UC Regents approved plans for a 15-year, $2.5 billion program to redevelop the Hillcrest medical campus.

Funding for research has increased, year after year. In fiscal year 2022, the university earned a record $1.64 billion in research funding, up 6 percent from the previous year and the 13th consecutive year that research funding has topped $1 billion annually. Health Sciences accounts for the majority of that funding: more than $835 million in 2022.

Although one of the youngest in the nation, UC San Diego School of Medicine is ranked fifth in the country among public medical schools for National Institutes of Health (NIH) funding.

In terms of philanthropy, giving to UC San Diego Health Sciences has been equally robust, involving thousands of individual donors and total gifts sometimes exceeding $200 million in a single year.

"My approach to philanthropy has been simple and straightforward," said Brenner. "Everyone needs support, but we must prove that we are deserving of support. I loved sharing our vision and accomplishments and asking people to participate in our transformative venture.

"My entire career has been at public and private academic health institutions. My career has always involved education, research, patient care, outreach and administration. I believe that these aspects should be synergistic, and I have always pushed to make significant contributions wherever I am."

UC San Diego Chancellor **Pradeep K. Khosla** agreed:

"There can be no disputing the incredibly important advances and growth that have occurred under David's watch and leadership. Back in 2007, he returned to UC San Diego charged with leading Health Sciences in all manner of ways: as a researcher, physician and educator. He has succeeded beyond all expectations, and always with that characteristic enthusiasm, drive and vision."

Lessons and recollections

BRENNER CREDITS OTHERS FOR MANY OF THE achievements during his tenure, such as **Jill Mesirov, PhD**, for expanding the use of data science and research computing as associate vice chancellor for computational health sciences; **Jerrold M. Olefsky, MD**, associate dean for scientific affairs, and **Christopher Glass, MD, PhD**, professor of cellular and molecular medicine, for their research strategies and recruitment; and **Gary Firestein, MD**, founding director of the ACTRI, which was launched in 2010 with a $37 million award from the NIH.

In 2015, ACTRI received a second NIH award of $52 million, and in 2020, a third for almost $55 million, bringing total funding support to approximately $144 million.

"Our ability to obtain funding is, in large part, a direct result of David's vision and support," said Firestein. "He provided the resources and encouragement needed for us to be competitive, which ultimately culminated in the ACTRI building. That support led to the creation of translational medicine as a medical discipline at UC San Diego and reversed a 'Wild West' culture that required everyone to build their own infrastructure for clinical research.

"Today, his vision is fully realized by rapidly growing clinical research and an institution that provides patients with access to novel therapies. From COVID-19 to Alzheimer's disease to cancer to autoimmunity, UC San Diego is now leading the way thanks to his vision."

Brenner notes with particular pride the creation of the Herbert Wertheim School of Public Health in 2019, the first new school on campus in 15 years. At Yale and Columbia, where he had worked previously, there were long-standing schools of public health. He thought UC San Diego should have one too.

Above: From mid-December 2020 to late-March 2021, UC San Diego Health operated a COVID-19 vaccination super station at Petco Park, dispensing more than 225,000 vaccine doses in 68 days. The program involved thousands of volunteers, faculty and staff. Top and bottom, David Brenner, MD, vaccinates drive-through patients, Middle: Brenner consults with Lydia Ikeda, associate chief operating officer, who oversaw vaccination efforts.

"We need to recognize and understand the value of preventive care on a large scale," said Brenner. "If nothing else, the pandemic made that very clear."

Brenner said his management style has always been to bring together the best thinkers and leaders, to work with them constantly but not micromanage, and to offer up a "dad joke" when necessary.

He cites among his proudest accomplishments the university's growing preeminence in computational biology, medical informatics and microbiome-based science.

"The emphasis has always been on becoming a leader, where great minds and talents come and stay. We've created numerous cross-campus collaborations. We're the only medical school with access to a supercomputer and a major (Jacobs) School of Engineering. And we have people here who are renowned in their fields, world leaders."

Brenner said his successor(s) will face familiar and entirely new challenges. Time and growth has spawned bureaucracy and sometimes burdensome politics. Competition is fiercer across the board. Burnout is a problem everywhere.

"We need to keep our momentum for improvement," he said. "We've proved we can function well during a pandemic. Now we must continue to do well by further expanding the health system and addressing issues like racial justice. From multidisciplinary excellence, we need to push for transdisciplinary programs—efforts that don't just combine excellence but create whole new fields."

What's next

DAVID BAILEY, MD, Distinguished Professor of Pathology and Pharmacy, Emeritus, can claim a particular perspective in assessing Brenner's tenure. Bailey twice served as interim dean of the School of Medicine, first in 1999-2000 and again in 2006-2007, preceding the arrival of Brenner.

"Dr. Brenner is the longest-service vice chancellor for Health Sciences in UC San Diego history, and among the longest serving at his position currently in the nation," said Bailey, who published "Catching the Wave," a history of the School of Medicine in 2017.

"On his watch, remarkable achievements were made, including the most successful fundraising Health Sciences has ever had, greater diversity of leaders, a new school of public health, recruitment of renowned scientists and, all the while, maintaining his own outstanding research program. That's unusual. Most people in his position curtail or give up their research completely."

Initially, after stepping down as vice chancellor, Brenner planned to return to his lab and teaching.

"I'll have more time to devote to research, to go deeper. It's an opportunity to reach out to the best scientists and dig into the best science," said Brenner, whose published papers in recent years have ranged from genetic variants in amyotrophic lateral sclerosis to wastewater screening for SARS-CoV-2 variants to the molecular drivers of liver disease.

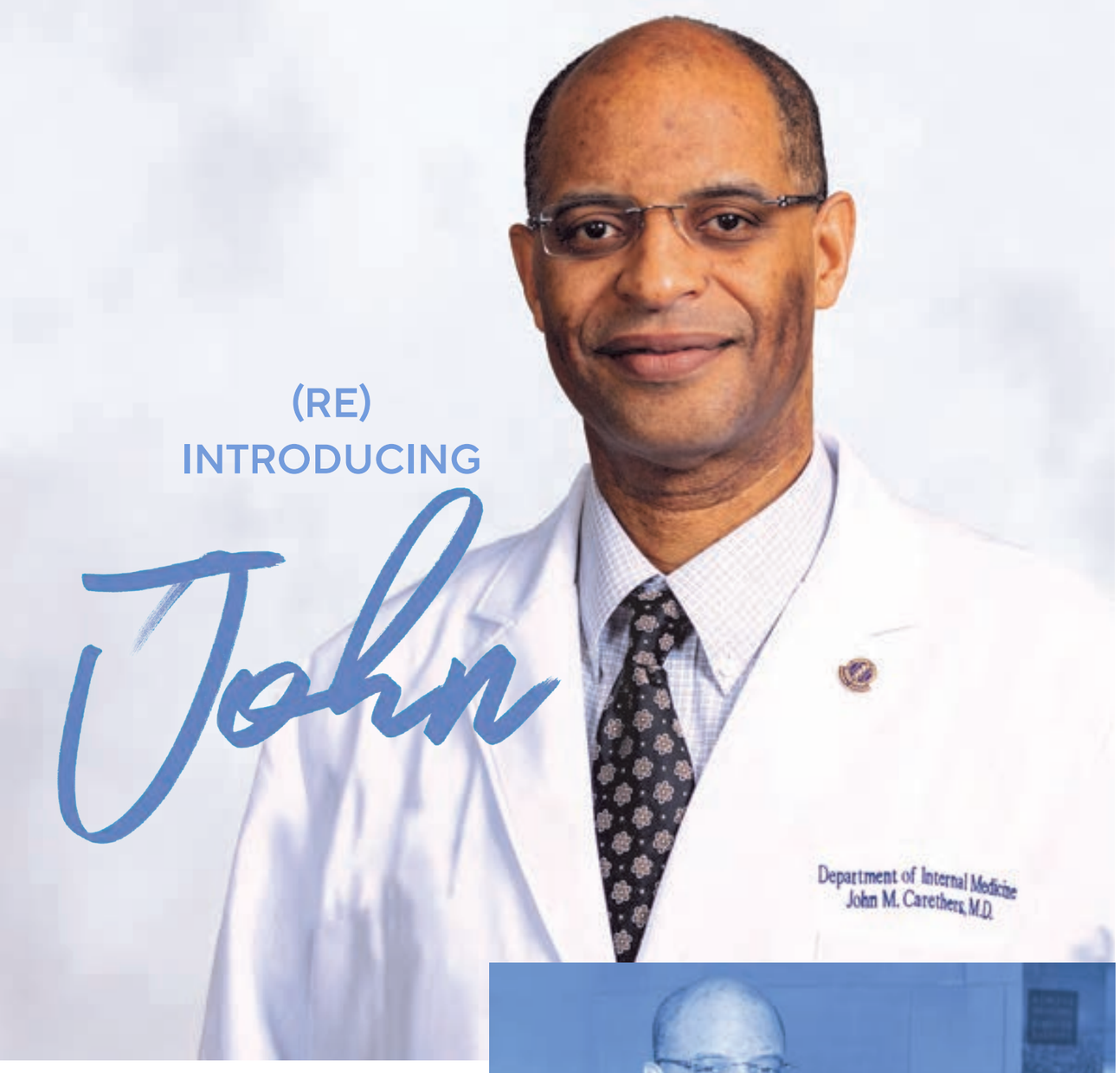
But Brenner left open the possibility of other opportunities, and one arrived last September when Sanford Burnham Prebys, a nonprofit medical research institute located just a few miles up North Torrey Pines Road from UC San Diego, announced that Brenner would become its next president and CEO.

"I've known about SBP for many years," said Brenner. "I have worked with its leaders and faculty many times over those years. They have so much to offer. It's a culture of encouraging scientists to pursue opportunities and to collaborate with others to achieve incredible goals," Brenner said. ●

CV highlights

- Served as UC San Diego's seventh vice chancellor for Health Sciences and the 14th dean of the School of Medicine from 2007-2022, more than twice as long as any predecessor.
- Previously served as chair of the Department of Medicine and Physician-in-Chief of New York Presbyterian Hospital/Columbia University and, before that, at University of North Carolina at Chapel Hill.
- Received his MD from Yale University School of Medicine in 1979.
- Completed his residency in Internal Medicine at Yale-New Haven Medical Center in 1985 and his gastroenterology fellowship at UC San Diego in 1986.
- Published roughly 200 peer-reviewed papers and owns two patents.
- Elected to the National Academy of Medicine; president of the Association of American Physicians; editor of *Gastroenterology* from 2001 to 2006.
- Member of the 2021 Highly Cited Researchers by Web of Science and Clarivate Analytics, the only vice chancellor to be recognized for this highest level of research productivity.

(RE) INTRODUCING John



Transformation continues under the leadership of the new vice chancellor for Health Sciences, John Carethers.

BY NICOLE MLYNARYK

Above: John Carethers, MD, and his wife, Denise.

> "I've never seen so many people excited to see someone come back."
>
> CLEMENT RICHARD BOLAND, JR., MD

JOHN M. CARETHERS, MD, IS MANY THINGS: physician, scientist, teacher, mentor, husband, father, friend and role model.

He's also the new vice chancellor for Health Sciences at UC San Diego.

The Michigan-born gastroenterologist has largely split his career between the Midwest and Southern California, including a stint as a professor in the Division of Gastroenterology at UC San Diego School of Medicine. He returns 13 years later to lead the growing academic and clinical enterprise.

As vice chancellor, Carethers will drive the overarching strategy for all of Health Sciences, fostering research collaborations, expanding the health care system, enhancing educational opportunities and bolstering philanthropic support. His collaborative approach and modern point of view are well suited to UC San Diego's vision and pursuit of innovation.

A quick scan of his CV makes the following clear: Carethers is endlessly hardworking, disciplined, curious, courageous and always challenging himself and his field to be the best.

But talk to his peers and another theme emerges: Carethers is a people person. He knows names and faces. He visits clinical sites and faculty offices. His door is open, and he is generous with his time.

"He makes you feel like you're the only person in the room," said **Thomas J. Savides, MD**, chief of the Division of Gastroenterology at UC San Diego School of Medicine. "John has this rare combination of extreme intelligence, integrity and warmth that makes him a unique leader. You can't help but want to be more like him."

These features go beyond personality. They are fundamental to Carethers' approach to leadership. It's what propelled him through the ranks during his initial 15 years at UC San Diego, and guided his recent 13-year tenure as chair of the Department of Internal Medicine at University of Michigan Medical School.

"In order to lead, you first have to listen," said Carethers. "You have to understand the issues and gain people's trust."

In the next few months, Carethers aims to do just that. While getting to know the new schools, buildings, faculty and staff, he'll gather ideas for the collective vision of Health Sciences.

"No one person can fix every issue," he said, "but I will certainly listen and try."

Rising Star

CARETHERS' STORY BEGINS in Detroit, Michigan, where he was born the 10th of 12 children to parents James and Eleanor. In the Carethers household, education was key. Carethers' dream of becoming a doctor was inspired by early explorations of the family's encyclopedia collection. Over the years, the Carethers siblings have collectively obtained 17 college degrees, all earned through the support of scholarships, grants and loans. John Carethers continued to live at home and work nearly 30 hours a week to put himself through college at nearby Wayne State University, where he also attended medical school.

This strong work ethic and fervent curiosity carried into his clinical studies. Carethers finished at the top of his medical school graduating class, and subsequently matched at the nation's leading internal medicine residency program: Massachusetts General Hospital. It was there, through complex patient cases and early exposure to clinical research, that Carethers narrowed his focus to gastrointestinal oncology and committed to pursuing a career in academic medicine.

These decisions led to his first return to the Midwest, where he joined the University of Michigan's gastroenterology fellowship program. The move would prove to be influential in many ways, particularly in introducing him to two important figures: his lifelong mentor and his wife.

Clement Richard Boland, Jr., MD, was already a world leader in hereditary colon cancer research. His lab was flourishing amid recent revolutions in genetics and molecular biology, which generated new research tools that Carethers picked up with ease.

"John was already a superb physician when I met him, but it wasn't long before he was also a fantastic translational researcher," said Boland. "He dove headfirst into the trickiest questions in tumor biology and soon made a series of key observations that fueled both of our careers."

When Boland was recruited to UC San Diego in 1995, he knew he wanted to bring Carethers along with him. But by this point, the rising star was traveling as a pair.

Only days into his fellowship, John met Denise, a nurse practitioner who was also training at the university. Days before his fellowship ended, the two wed.

"So it was really Denise that had to be recruited," said Carethers. But San Diego soon became the couple's home and the birthplace of their four daughters, affectionately known as 'the Carethers girls.'

"He absolutely adores his wife and daughters," said Boland, who became a close family friend during this period, often babysitting the girls and eventually becoming godfather to the youngest. "We shared a common belief in the power of family, and the ways it can ground you through the ups and downs of academia."

From the start, Carethers' career at UC San Diego seemed destined to skyrocket. His research was booming, following early discoveries on DNA mismatch repair and its effects on tumor progression. This work expanded to include tumor genetics, biomarker discovery and the role of

inflammation in molecular pathology. More recently, Carethers has pioneered studies on racial disparities in colorectal cancer, studying the biological and social risk factors contributing to patient outcomes.

Carethers also maintained a clinical practice during this time, continuing to treat high-risk cases of colon cancer and patients with familial genetic syndromes. In the classroom, his work with students resulted in numerous teaching awards.

So when Boland was recruited out of state, Carethers became an obvious candidate to take his place as chief of the Division of Gastroenterology. As the youngest faculty member to assume the role at UC San Diego, Carethers quickly proved his potential as a leader in academic medicine.

During his tenure from 2004 to 2009, Carethers doubled the division's faculty size, its clinical revenue and its National Institutes of Health grant portfolio. The gastroenterology fellowship program grew significantly, and the division's scope expanded to include pediatric gastroenterology. Carethers also secured the inaugural Gastroenterology Center grant, which allowed the division to partner with other local institutions, including the La Jolla Institute for Immunology, The Scripps Research Institute and Sanford Burnham Prebys Medical Discovery Institute.

Key to each of these successes were Carethers' strengths in uniting his team. "He's uniquely skilled at building consensus and collaboration among disparate groups, and he does so with such ease and poise," said Savides, who was named to the gastroenterology chief role in 2021.

> "I've gained a lot of experience since I was here last, so I'm excited to return and give back to this incredible team."
>
> JOHN CARETHERS, MD

New Heights

IT DIDN'T TAKE LONG FOR INSTITUTIONS ACROSS the country to recognize Carethers' achievements and attempt to recruit him. When he decided it was time for a new challenge, Carethers chose to return to his home state and serve as chair of the Department of Internal Medicine at University of Michigan.

In that role, Carethers oversaw 930 faculty and more than 1,000 departmental staff. He managed a $400 million annual budget, $250 million in annual external research grants and the integration of the department within the $5.8 billion University of Michigan Health System. Much like UC San Diego Health, the campus saw a significant physical expansion and a renewed emphasis on primary care during this time.

One of the areas of progress that Carethers is most proud of is his work in faculty affairs. Under his leadership, new programs offered training in biostatistics and how to launch clinical trials. Junior faculty endowments supported new hires, and faculty wellness programs fought against burnout. Through a new Clinical Excellence Society, faculty who demonstrated particular excellence toward patients and colleagues were formally recognized.

"My overarching goal is to promote the faculty in my department in what they do," said Carethers.

If his mentoring legacy is any indication of his success, the long list of students and fellows he's overseen speaks for itself. Many of Carethers' trainees now hold leadership positions at major universities and in federal institutions. Many are women or members of other historically excluded groups.

"John brings out the best in people," said Boland. At a gastroenterology conference, Boland found himself in a huddle of UC San Diego colleagues when the conversation turned to the topic of Carethers. A junior faculty member in the circle perked up to share a story.

While preparing a major grant application early in her career, she sent a message to the team at Moores Cancer Center asking if anyone had experience with this particular award.

"Not only did John respond, but he showed up at her office with a copy of his grant in hand, ready to help her with her application," said Boland. "To have that kind of support from your boss and know that someone's really pulling for you, that's what John provides, and it stays with people."

Right: As chief of the growing Division of Gastroenterology at UC San Diego School of Medicine, Carethers (center-right) gathers with faculty in 2008.

What's next

AFTER TREMENDOUS SUCCESS AS DEPARTMENT chief, Carethers decided he was ready for the next opportunity. Across the country, UC San Diego leaders were beginning their national search for a new vice chancellor. The timing was fortuitous.

"I've never seen so many people excited to see someone come back," said Boland, who made his own return to UC San Diego in 2017 as a professor of medicine.

"San Diego has always had a special place in my heart," said Carethers. "I've gained a lot of experience since I was here last, so I'm excited to return and give back to this incredible team."

As his vision for Health Sciences continues to take shape, Carethers notes several areas he's already looking forward to addressing.

In research, he plans to focus on the need for more research space and facilitate increased collaboration between Health Sciences and other departments and schools on campus.

"A recent evolution in the field has been the use of huge datasets analyzed with bioinformatics and artificial intelligence tools," said Boland. "If we're going to stay on the cutting edge, we need a leader like John who can recruit new talent with fresh ideas, learn what these experts need, and help us all adapt and grow together."

Carethers also hopes to increase research activity among clinicians and maintain an economic engine to support this. "Research and clinical care are symbiotic, both in practice and in economics, so we need to encourage and support that with transparency," Carethers said.

Other immediate goals include raising funds to ensure that the quality and quantity of clinical services are maintained throughout the renovation of the UC San Diego Medical Center in Hillcrest. Carethers is excited to meet leaders and encourage further growth at the Herbert Wertheim School of Public Health and Human Longevity Science and Skaggs School of Pharmacy and Pharmaceutical Sciences.

In education, Carethers is committed to attracting the most outstanding medical school students, and strengthening philanthropy and scholarships to make that happen. "Our students are the future, and if we want a bright and diverse group of trainees, we need to provide competitive scholarships to attract those from all sorts of economic backgrounds," he said.

Carethers takes a similar approach to equity, diversity and inclusion among faculty and staff.

"We need to ensure there are consistent processes in place for faculty hiring, evaluation and retention," he said. "It's about creating an equitable and amiable culture, and then holding people accountable to it."

"The fact that we have an African American at the top is really important," said Boland. "Who can speak to racial disparities with more authority than someone who's been there? Who can create a comfortable, equitable environment like someone who knows what it's like to be in the minority? He's just the right guy for this kind of change."

For many, Carethers' arrival represents a chance to realign and reassess in preparation for the next chapter in Health Sciences history.

"UC San Diego has grown and transformed tremendously in recent years, so this is an opportunity to take a fresh look at our organization and how we can ensure all faculty members feel included, heard and valued," said Savides. "John Carethers is the perfect person to lead us through that process and into our future." ●

CV highlights

- Serving as UC San Diego's eighth vice chancellor for Health Sciences.
- Previously served as the C. Richard Boland Distinguished University Professor, the John G. Searle Professor and chair of the Department of Internal Medicine at University of Michigan from 2009-2022.
- Received his MD from Wayne State University School of Medicine in 1989.
- Completed his residency in Internal Medicine at Massachusetts General Hospital in 1992 and his gastroenterology fellowship at University of Michigan in 1995.
- Published roughly 300 peer-reviewed papers.
- Elected to the National Academy of Medicine and the American Academy of Arts and Sciences; president of the American Association of Physicians and the American Gastroenterological Association; editor of *Gastroenterology*.
- As chair of the Minorities in Research Council of the American Association for Cancer Research (AACR), contributed to the AACR Cancer Health Disparities Report and its presentation to the U.S. Congress.

RE IMAGINING PUBLIC HEALTH

BY YADIRA GALINDO

From pandemics to health inequities, confronting future crises will look different—and that's a good thing.

Shane Abbasi (center) shares his research with public health students and faculty.

UNLIKE MANY OF HIS PEERS, SHANE ABBASI enrolled at a community college as an undeclared major. An immigrant, first-generation college student from a low-income school district, he had an interest in health care but lacked previous exposure to educational and career options. In his freshman year, Abbasi considered psychology and human behavior but felt the focus was too narrow.

Following advice from an academic advisor in his sophomore year, Abbasi chose public health as a major and enrolled at the Herbert Wertheim School of Public Health and Human Longevity Science at UC San Diego, where he got a multidimensional view of health that included physical and mental health, healthy policy, environmental factors, and cultural practices and behaviors.

"I was blown away by the way public health empowers students, educators and practitioners to roll up their sleeves and work tirelessly to reach communities and transform our 'sick care' system to a health care system," said Abbasi, now a senior in the Bachelor of Science in Public Health (BSPH) program in the '21-'22 academic year. "This changed my life, and it's where my passion for public health began, a passion that was later confirmed by a deadly global pandemic."

With seven education programs, the Herbert Wertheim School of Public Health is cultivating the next generation of diverse public health professionals and leaders through innovative and transformational education programs that include bachelor's, master's and doctoral degrees as well as a preventive medicine residency.

At an especially critical time, the founding of the school of public health allows UC San Diego to leverage its search strengths to address deep and pressing 21st-century public health issues locally and globally — and train the next generation of public health practitioners and researchers.

"No matter the public health challenge, whether it is infectious diseases, health equity, climate change, aging or chronic diseases, our community and our campus have a new partner to help design multipronged solutions to contemporary health problems," said **Cheryl A.M. Anderson, PhD**, professor and founding dean of the Herbert Wertheim School of Public Health.

In 2020, as the school was being primed for its first academic year, it quickly became apparent that it would need to pivot its public health efforts to help mitigate the impact of the COVID-19 pandemic.

The pandemic underscored something Anderson already knew: Major public health challenges require a coordinated, tranformational approach with a public health lens that is informed through community partnerships and collaborations with scientists in other fields, such as medicine, social sciences and engineering.

The Herbert Wertheim School of Public Health was involved in Return to Learn, a bold initiative to return students to the UC San Diego campus and in-class learning during the pandemic. The school partnered with the San Diego County Department of Public Health for contact tracing and contributed to the design and implementation of CA Notify — California's COVID-19 exposure notification system using smartphone technology.

"The school dove deeper into health disparities intensified by the pandemic by addressing the clinical needs of thousands of new asylum seekers at the San Diego/Tijuana, Mexico, border. With community partners, researchers investigated the negative impacts of COVID-19 on established refugee communities in San Diego.

"The school of public health is at its best when our training and research efforts, as well as our community academic partnerships, are working together in a way that acknowledges the importance of diversity to true excellence and innovation," said Anderson, who is also the inaugural Hood Family Endowed Dean's Chair in Public Health.

"This school is not only built for those of us who are walking through the halls in the present moment but we are keenly aware of our need to be relevant decades from now. That means we need to recruit a diverse and inclusive type of scientist to train here and to work here."

DIVERSITY IN RESEARCH

THE HERBERT WERTHEIM SCHOOL OF PUBLIC Health launched with a core mission of "radical hospitality and inclusivity," centering justice, equity, diversity and inclusion (JEDI) in its approach to public health research, education and service.

Among the many programs aimed at addressing JEDI is a National Institute of Aging-funded R25 undergraduate training program called Mentorship for Advancing Diversity in Undergraduate Research on Aging (MADURA). Its primary objective is to improve diversity in research and clinical careers that are focused on Alzheimer's disease and related dementias and other aging-related topics by providing paid hands-on research experience to 27 UC San Diego undergraduate students who are from groups historically underrepresented in medical, science, technology, engineering and mathematics (MSTEM) majors.

"We want to enable students in medical and STEM majors to enter careers they aspire to and where better representation is needed. MADURA addresses the needs of the students through mentoring, research experience and financial support, but it also addresses important scientific research needs," said **Sheri Thompson, PhD**, MADURA program coordinator.

"By having a more diverse population of research professionals, our hope is that the quality and the nature of research on diseases such as Alzheimer's will improve and we will be more inclusive of groups who have been overlooked."

With an interdisciplinary approach to public health, MADURA has 30 faculty mentors ready to help students with a range of majors from psychology to cognitive science to computer science.

"MADURA has changed how I think about health care in the need for diversity in research," said **Nicolaas Ugalde**, who participated in MADURA as a senior and graduated with a Bachelor of Science in General Biology in June 2022.

"I had no idea that a lot of research mainly focuses on Caucasians. But there are some differences in health care between races. For example, dementia and aging happen at different paces," said Ugalde, who has ambitions of becoming a neurosurgeon. "I learned, being a Latino, that we age slower. I've seen it with my grandmother, who recently started showing signs of dementia at 96."

After the pandemic necessitated two years of virtual-only labs, Ugalde was ecstatic to have the opportunity to work in a wet lab. During his training, he attended the lab of **Matthew Shtrahman, MD, PhD**, in the Department of Neurosciences, who is investigating causes of neurodegeneration.

"These are experiences I may never have had without MADURA," said Ugalde. "I could have gone my entire life just doing clinical work. When I'm in my residency, I'm going to look at patients differently, individually, and not just generalize."

In addition to hands-on experience, the program supports trainee academic success and retention and promotes application to graduate and medical programs as well as entry into clinical or research careers in aging or Alzheimer's disease and related dementias.

"UC San Diego is a unique place for a program like MADURA because we have one of the largest neuroscience programs in the world and we have the Herbert Wertheim School of Public Health and Human Longevity Science," said **Steven Edland, PhD,** MADURA principal investigator.

"Students graduating from the MADURA program have the tremendous advantage of having real-world job experience that will help them apply to graduate or medical schools and obtain research jobs out of college."

In its first academic year – 2020-2021 – the school held classes amid a pandemic, but students, faculty and staff were also impacted by an intense national conversation about anti-Black racism and structural and systemic racism faced by others. This context shaped the curriculum and demanded dramatic changes to teaching, learning and living.

CHERYL A.M. ANDERSON, PHD

"The school of public health is at its best when our training and research efforts, as well as our community academic partnerships, are working together in a way that acknowledges the importance of diversity to true excellence and innovation."

"We have learned some important lessons during the pandemic. It became critically clear, as the dean of a new school of public health, that a conversation about racism had to be foundational to what we did in this new school if we are really going to dismantle the systems and the structures that promote racism and, as a result, promote less-than-optimal health outcomes across all of society," said Anderson.

An early component was to invite all employees to participate in a 24-hour racial resilience seminar series that helped participants recognize systems that normalize racism, explore an individual's role in perpetuating structural racism, talk compassionately about it and make sustainable changes that build a school with a harmonious foundation.

Systemic racism seemed to be making headlines daily. In a five-month period in 2020, in five separate incidents, five Black people were killed: Ahmaud Arbery, Breonna Taylor, Daniel Prude, George Floyd and Rayshard Brooks. Sadly, more incidents would follow, including rising violence against people of Asian descent.

To create a safe space for difficult conversations, the Compassionate Action Circle was introduced.

"We are all being impacted by these events. They impact our well-being, our productivity and our sense of safety and belonging," said **Martha Anderson, JD, MDiv**, dean's chief of staff.

"The Compassionate Action Circle is an approach to create a place where wellness is supported. We talked about steps to take when you are in a system that, by design, is oppressive to some people. What are the measures we can take to free all people from oppression that is perpetrated in the environment?"

Held in October 2021, the forum facilitated an open conversation that was needed to build a sense of community, said **Kyle Choi**, informatics project manager in the Herbert Wertheim School of Public Health.

"The Compassionate Action Circle was held during a time when many of our staff were only seeing UC San Diego's reactionary-like responses to JEDI-related current events," said Choi. "The forum was perceived as more of an intentional and proactive effort."

The Compassionate Action Circle adds a unique aspect to the school, which is the fostering of compassion into the academic space, said **Sonia Jain, PhD**, interim associate dean for Justice, Equity, Diversity, and Inclusion.

"Our students are impacted too. After the George Floyd incident, I put aside what I was planning to teach that day to have a conversation, a moment of healing," said Jain. "We need a place to talk about the underlying issues of how it affects the principles of JEDI across the school, whether you are a student, faculty or staff."

"The hope is that the Compassionate Action Circle and similar programs become part of the community so that when incidents happen, which unfortunately continue to occur, our school has a safe place to communicate."

EXPERIENTIAL LEARNING

APPLYING JEDI PRINCIPLES WITHIN THE WALLS

of the school may lead to more inclusive and healthier work and learning environments, but learning to apply them to the practice of public health is another undertaking altogether.

Abbasi was 13 years old when his family immigrated to the United States. Both of his parents had underlying health conditions; navigating the health care system was difficult.

"We faced many challenges, such as lack of health insurance, lack of information, cultural and linguistic barriers, and discrimination. At such a young age, I had to take on the role of an interpreter for my family. It became my responsibility to find their doctors, make their appointments, take time from school to be present during their appointments and more," said Abbasi, who was struggling with a new language and culture himself.

"Unfortunately, from those interactions, I realized that many physicians in the United States failed to consider our background and culture in their care. They simply looked at us as charts and diagnoses instead of practicing in the context of family, culture and community."

Abbasi, who was one of 20 students in the BSPH Honors Practicum in his senior year, credits the program and other public health classes with helping him understand how social determinants of health affect individuals and the importance of looking at the big picture. He plans to apply this in a future career in medicine.

"If a child walks into my clinic with an infection, instead of prescribing antibiotics right away, I will also find out if that child has enough food at home. Is he or she living with 14 other people in a one-bedroom apartment? Are there any cultural or language barriers that do not allow my patient or their family to understand their prescriptions? Can they afford transportation to my clinic and back?" said Abbasi.

"Instead of just putting a Band-Aid on their conditions, studying public health has taught me that it is also my duty to prevent future health issues before they even start."

The BSPH program has grown from 400 students to more than 600 since the department of public health became a school. Students must apply to be part of the rigorous BSPH Honors Practicum, which spans three-quarters of a student's senior year. Only 20 are selected.

Nancy Binkin, MD, MPH, director of the BSPH Honors Practicum, looks for students who will apply the public health skills they learn in the program in their careers.

She selects stakeholder-driven, community-based public health programs to train students in teamwork and community service. In the 2021-2022 academic year, students helped a San Diego County school district evaluate teacher burnout during COVID-19 and provided the district with practical steps to combat it.

Another group worked with the Orange and Riverside counties to assess drowning surveillance systems to identify the data collection necessary for an effective system. Another team worked with the UC San Diego Academic Integrity Office to identify students' perceptions on cheating on campus, how often they observe it and how likely they are to report it.

Students work directly with stakeholders, as they would if they were employees. Binkin requires perfection from their projects, and she finds great satisfaction in pushing students to perform beyond what is typically expected from an undergraduate program.

VICTORIA OJEDA, PHD, MPH

"The practicum makes students active participants in our communities by applying what they're learning in the classroom in real-world public health settings."

"This is what you leave behind in the world: the next generation who have an appreciation for public health and go on to do things you could never dream of doing," said Binkin. "I get such energy out of being with these young folks, and I feel that I am able to shape their careers. I get to do a lot of one-on-one mentoring of really talented young people."

In addition to the BSPH program, residents in the General Preventive Medicine Residency participate in practicum rotations that train them in three areas: clinical preventive medicine, population-based medicine and research.

The Master of Public Health (MPH) program, which had a record 52 students in the 2021 cohort, up from 21 in 2018, requires all students to participate in a field-based or population-based practicum. Students pick projects relevant to current public health concerns, said **Victoria Ojeda, PhD, MPH**, director of the MPH practicum.

"The practicum makes students active participants in our communities by applying what they're learning in the classroom in real-world public health settings," said Ojeda.

"During these practical experiences, they receive mentorship from professionals who are working on important public health issues. We hope this will help them make career decisions on whether to go down one trajectory or another."

MPH students have diverse backgrounds. Some have started their studies after earning their bachelor's degree, but others are mid-career professionals who want additional training.

"As a new school of public health, we have committed to doing things differently from traditional schools and to take on new issues with greater priority than traditional schools give them," said Michael Pratt, MD, MPH, professor, interim assistant dean for graduate education and director of the MPH program.

COVID-19 created both challenges and opportunities for the practicum, as many organizations reduced workloads to essential employees only or transitioned to remote work, limiting students' ability to gain hands-on experience.

But UC San Diego's active COVID-19 response offered unexpected training directly with the university's research and community programs.

"Students at UC San Diego have access to top-notch translational research and community-based activities," said Ojeda. "We are strongly positioned with ties to the community. And our location near the U.S.-Mexico border allows students to address issues and have experiences that they might not get at other schools. It makes for a very rich learning environment." ●

A NEW PHASE

BY SCOTT LAFEE

EMERGING TECHNOLOGIES, SOCIAL IMPERATIVES AND THE NEXT PANDEMIC ARE CHANGING HOW CLINICAL TRIALS LOOK AND WORK.

DURING HIS REIGN (605 BC-562 BC), NEBUCHADnezzar II, King of Babylon, Sumer, Akkad and all of the universe, decided that a diet consisting entirely of meat and wine ensured good health, and so ordered his subjects to eat nothing more or less.

Not everyone agreed, and Nebuchadnezzar, perhaps curious, permitted a dissenting group to consume a diet of just legumes and water. After 10 days, the data was in: The legume-eaters were clearly better nourished than the meat-eaters.

Chronicled in the Bible's book of Daniel, Nebuchadnezzar's experiment marks perhaps the first documented clinical trial in human history, though the evolutionary path to today's gold standard—a randomized, double-blinded, placebo-controlled clinical trial—has required several centuries of constant change and improvement.

The COVID-19 pandemic was, in some ways, another inflection point. Among all of the other ways that the pandemic altered how we live and think, it prompted new reassessments and reimaginings of how clinical trials can and should be conducted.

With unprecedented speed and scope, a pair of vaccines based on messenger RNA (mRNA) technology from Pfizer-BioNTech and Moderna sped through testing to receive emergency use approval (EUA) in a fraction of the time historically required. They have since inoculated more than 1 billion people around the world to prevent or reduce harm or death from infection by the SARS-CoV-2 virus that causes COVID-19.

Emerging alternatives and changes:

Adaptive trials that can be altered in process as treatments and conditions change

The use of real-world data derived from electronic health records (EHRs)

"In silico" trials based on computer simulations in combination with EHR information

Open-label trials in which both health providers and patients are aware of the drug or treatment given

The use of surrogate biomarkers, such as the presence or absence of a specific molecule in the blood, as milestones for approval, rather than clinical endpoints

Trials under the Food and Drug Administration's "animal rule" when human trials are not possible

"The pandemic demonstrated that clinical trials can be performed rapidly and safely when there is a crisis, when sufficient numbers of people are affected, and the Food and Drug Administration (FDA) and other governmental organizations recognize the urgency," said **Stephen Spector, MD**, Distinguished Professor of Pediatrics in the UC San Diego School of Medicine and principal investigator for the UC San Diego arm of the Moderna trial.

"Not every study can be performed with this level of efficiency, but lessons have been learned that, when applied to current and future studies, can help to expedite the review and approval of important new investigational vaccines and drugs."

At the height of the pandemic, the seeming alacrity with which the COVID-19 mRNA vaccines raced to EUA alarmed many, who feared the process was too rushed and the science too uncertain, though the Commonwealth Fund later estimated that the U.S. vaccination program prevented more than 1.1 million deaths and 10.3 million hospitalizations.

"Our estimates suggest that in 2021 alone, the vaccination program prevented a potentially catastrophic flood of patients requiring hospitalization. It is difficult to imagine how hospitals would have coped had they been faced with 10 million people sick enough to require admission," wrote Commonwealth Fund authors.

"In addition to reducing hospitalization and death, vaccination prevented many millions of COVID infections, reducing the prospect that millions of Americans could develop long COVID and its debilitating symptoms."

The indisputable success story of the mRNA COVID-19 vaccines—and the particulars of how they were put into effect so quickly—has added fuel to ongoing debates about the nature and processes of clinical trials, and, most notably, how they can, should and need to change.

Accelerating clinical trials

UC SAN DIEGO HEALTH RESEARCHERS AND physicians oversee and manage hundreds of new and ongoing clinical trials each year. There are more than 1,000 currently listed on its website at clinicaltrials.ucsd.edu. No institution in the region conducts more trials across a broader spectrum of diseases, treatments and conditions. No institution is working harder to make them more effective.

"The traditional double-blind, placebo-controlled trial is still the gold standard, but alternatives are emerging," said **Gary S. Firestein, MD**, director of the Altman Clinical and Translational Research Institute at UC San Diego, which provides scientific, clinical, administrative and logistical support to clinical trials at UC San Diego.

(A double-blind study is one in which neither the participants nor the researchers know who is receiving treatment or a placebo. The goal is to minimize expectation bias, which leads patients or doctors to observe improvement even though a "dummy" medicine is given.)

Before a new drug or treatment can reach the market, it must pass through several stages of testing and assessment, beginning with preclinical research, which alone can take years, sometimes decades. One reason the mRNA COVID-19 vaccines could be put into clinical trials was the fact that the approach had already been the subject of years of research and testing for other diseases.

Generally speaking, it takes seven to 10 years for a clinical trial to successfully move through all four phases (see sidebar), though longer is not uncommon. Many attempts have been made to shorten the process.

In 2016, for example, Congress passed the 21st Century Cures Act, partly aimed at streamlining drug and device approval. Some public officials and others, then and now, argued for simply truncating trials, suggesting that promising new drugs could be released to the public after satisfying only basic safety requirements.

In 2017, Jim O'Neill, a former official at the U.S. Department of Health & Human Services declared, "Let's prove efficacy after they've been legalized."

Most experts don't go that far.

"Shortening clinical trials has the potential to move interventions through the study phase too quickly. Interventions may have outcomes that cannot be detected in a trial that lasts weeks rather than years," said **Anthony Magit, MD**, professor of surgery and medical director of the Office of IRB Administration at UC San Diego.

Types of Clinical Studies

01.

Observational Studies
Generally involve collecting information about people in normal settings, such as how medical conditions change over time based on exams and questionnaires.

02.

Clinical Trials
More narrowly focused to answer specific questions, such as whether a new drug or medical device is safe and effective

"With innovative study design, including better characterization of subjects, fewer subjects may need to be enrolled, but longer studies may be necessary to assess a broader range of outcomes. Long-term follow-up after approval for clinical care may be an important component to evaluate sustained benefit and to monitor for negative outcomes."

Clinical trials for the breast cancer drug tamoxifen, for example, began in the 1970s; late-stage trials are ongoing.

Some experts have advocated for modifying the third phase of clinical trials, which they deem unnecessarily time-consuming, expensive and redundant. They favor "adaptive licensing," especially for promising therapeutics that address critical or urgent needs, such as new vaccines, antibiotics, cancer medications or therapies for Alzheimer's disease.

These drugs would be rolled out sooner and faster, beginning with limited distribution to the sickest patients after conclusion of Phase I. Early recipients would be monitored, and

> "SHORTENING CLINICAL TRIALS HAS THE POTENTIAL TO MOVE INTERVENTIONS THROUGH THE STUDY PHASE TOO QUICKLY. INTERVENTIONS MAY HAVE OUTCOMES THAT CANNOT BE DETECTED IN A TRIAL THAT LASTS WEEKS RATHER THAN YEARS."
>
> ANTHONY MAGIT, MD

Clinical Trials Defined

PHASE I

An experimental study on a small (less than 100) group of usually healthy participants to assess safety and possible side effects and, in the case of drugs and vaccines, determine the likely correct dosage.

PHASE II

A larger study (100 to 300 participants) that examines efficacy: Does the drug work in people with the targeted disease or condition? Safety monitoring continues as well. These trials often last a couple of years and establish clinical proof of concept.

PHASE III

The final trial before possible approval, and the largest, with hundreds to thousands of participants reflecting different demographics and perhaps involving different drug dosages or combinations with other drugs. The goal is to best approximate whether the tested product is broadly safe and effective, and ready for market pending approval by the FDA.

PHASE IV

A study after FDA approval to monitor a drug or device's long-term efficacy in large, diverse populations. These trials also look for side effects not seen in earlier phases.

if the drug appeared safe and effective, availability would be expanded to more categories of patients, a process dubbed "progressive reduction of uncertainty."

One problem is that safety signals might not be seen in limited trials, said Firestein, and effectiveness is not assured. This can create issues with third-party payers who bear the cost of expensive drugs that might not work.

Sandip Patel, MD, associate professor at UC San Diego School of Medicine and director of the clinical trials office at Moores Cancer Center at UC San Diego Health, is among those advocating for modified trials.

"In cancer clinical trials, there is a movement toward emphasizing novel therapeutic intent over a historical emphasis on statistical balance, which has improved access to trials," Patel said.

"With the current era focusing on approvals of novel therapeutics from Phase I in record time to help patients, such as the COVID-19 efforts, and continued vigilance throughout a drug's life cycle in both trials and real-world use, I think the old model of Phase I to Phase II to Phase III as discrete elements is a relic of the past."

At the HUMANOID Center of Research Excellence, the translational arm of the Institute for Network Medicine at UC San Diego School of Medicine, founding co-directors **Soumita Das, PhD**, and **Pradipta Ghosh, MD**, with staff director Courtney Tindle, talk about another way to tweak clinical trials. It starts with "Phase 0."

The current multiphase process is arduous but not necessarily productive, they say.

Most drugs fail somewhere along the pipeline, observed Das, many in the last phase because of a primary lack of efficacy. In other words, they never had a chance.

The HUMANOID approach leverages human organoids to model "diseases-in-a-dish." These multidimensional, multi-cell-type mini-organs can be a more realistic replication of complex human tissues than single-cell cultures or most animal models. (See P.68 for more on organoids.) If an experimental compound doesn't work in an organoid (Phase 0), it can be jettisoned with less waste of time and resources, said Das.

"HUMANOID's organoid-based models provide a head start on efficacy, giving researchers an incredible tool to separate useful therapies from dead ends. This is how we accelerate the drug discovery process and bring new hope to patients."

Fixing problems — at least some of them

I. DIVERSITY

The history of medical research is fraught with stories of women and minorities being either underrepresented or abused, such as in the notorious Tuskegee study in which researchers studied the effects of untreated syphilis in Black men over the course of 40 years.

By some estimates, as many as 90 percent of clinical trial participants have historically been white and of European descent, though disease clearly affects different people differently. A 2022 survey of more than 20,000 U.S.-based trials from 2000 to 2020 with published results found that less than half reported any race/ethnicity data. The majority of enrollees (mean 79.7 percent) were white, with all other race/ethnic groups underrepresented compared to census estimates.

"There is a push now to involve multiple sites and be inconclusive with respect to racial, ethnic and socioeconomic diversity to represent the diversity in society," said Magit. "A critical component of representing as much of society as possible is providing gender equity in clinical trial recruitment, as clinical trials have historically overrepresented males. One overall goal is to conduct clinical trials where the results are directly translatable to the affected population, rather than having to make adjustments due to narrow inclusion criteria or only including a subset of the affected population."

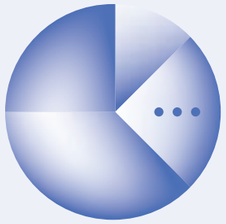
Diversity was an essential driver of the COVID-19 vaccine trials. The disease impacted people everywhere, but in the United States at least, it struck minority groups especially hard, with higher rates of hospitalization and death.

Spector noted that, with great effort, of the 336 study participants enrolled in the Moderna vaccine trial at UC San Diego, more than 50 percent represented minorities and persons of color.

Susan Little, MD, professor of medicine at UC San Diego School of Medicine and principal investigator for the UC San Diego study arms for two international COVID-19 vaccine trials (Astra-Zeneca and Johnson and Johnson) said the emphasis in both trials was increased participation in underserved communities, particularly those of color. These populations are traditionally underrepresented in clinical trials and remain overrepresented in rates of SARS-CoV-2 disease, hospitalization and death.

One visible way to do that, she said, was to create mobile clinics, including specially equipped vehicles, that brought vaccination opportunities to communities with residents unlikely or unable to visit the usual university-based testing sites. The clinics were often supported by local health care providers, adding familiarity and trust to the process.

> "THESE VEHICLES HELP OUR RESEARCH TEAM BRING VACCINE TRIAL OPPORTUNITIES TO HIGH-BURDEN COMMUNITIES THAT MIGHT OTHERWISE BE UNDERSERVED."
>
> SUSAN LITTLE, MD



II. GETTING DATA

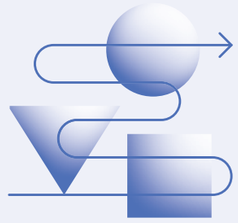
In 2014, Thomas Insel, MD, director of the National Institute of Mental Health (NIMH) from 2002 to 2015, noted that one of the reasons mental illness is so poorly understood is the lack of knowledge about the underlying brain mechanisms involved, including how they work or malfunction.

Insel introduced a new NIMH policy that requires clinical trials of psychiatric therapies to include basic research. That way, even if the trial fails, researchers might at least learn something about how the brain works.

Since his arrival at UC San Diego in 2016 to head the Alzheimer's Disease Cooperative Study (ADCS), **Howard Feldman, MD**, professor of neuroscience, has redirected efforts away from high-profile, large, late-stage clinical trials in Alzheimer's disease (which so far have had an extremely high failure rate and which have not resulted in an approved, market-ready, payer-supported treatment) to smaller, more nimble studies directed at achieving clinical proof of concept as a strategy to buy down risk of costly later-stage failures.

"We strive to keep focused on the highest-quality research and achievable research goals that answer important questions with approaches that will make a difference in the lives of our patients," said Feldman.

"At UC San Diego, we are ideally suited for collaborative academic-led clinical trials, taking on studies that are unlikely to be done by industry, or where ADCS might be an ideal partner. By contributing earlier-stage trials, each step successfully completed helps move us closer to our goal of benefiting persons at risk of or with Alzheimer's disease."



III. SHARING DATA

In 2007, the United States became the first nation to launch a database of clinical trial results involving drugs, devices and biologics, such as vaccines. The law described significant penalties for failure to comply, such as withholding of federal funding. The goal was to encourage sharing of information, especially if a trial failed, so that future research would be better informed.

It hasn't quite worked out as envisioned, even with a 2017 update in which the National Institutes of Health (NIH) and FDA enacted a "final rule" clarifying expectations and penalties. The results of many clinical trials remain unknown, especially for those that fail or fall short.

In 2020, for example, *Science* examined more than 4,700 trials whose results should have been posted to the ClinicalTrials.gov website. Reporting rates improved after the 2017 rule, but the journal still reported that hundreds of trials had not released data.

That's perhaps not surprising given that the overall likelihood of a clinical trial successfully moving from Phase I to market approval is less than 10 percent, with almost 70 percent of trials not making the jump from Phase II to Phase III.

"No one gets excited about publishing a negative result, and it is difficult to publish them in top journals," said Firestein, who noted, too, that trials that struggle or fail to accrue sufficient numbers of participants often lead to underpowered and suspect results.

Recruitment is an almost universal challenge. Eighty percent of trials are delayed or closed because of difficulties finding participants. Nine out of 10 trials double their original timeline in order to meet enrollment goals. One in 10 trial sites fails to enroll a single participant.

> "AT UC SAN DIEGO, WE ARE IDEALLY SUITED FOR COLLABORATIVE ACADEMIC-LED CLINICAL TRIALS TAKING ON STUDIES THAT ARE UNLIKELY TO BE DONE BY INDUSTRY."
>
> HOWARD FELDMAN, MD

IV. TREATING CHILDREN

The COVID-19 vaccines demonstrated a common medical challenge: approving life-saving vaccines and drugs for children. As of 2018, according to a study published in *Health Affairs*, 64 percent of new drugs were not approved for children despite laws and policies specifically intended to promote their development.

In fact, more than 30 percent of all prescriptions written for children involve off-label medications — the practice of using a drug to treat a disease or medical condition that it is not formally approved to treat.

"There is this fear that children are too fragile to be involved in clinical trials prior to FDA approval first in adults," said Spector. "However, for serious diseases, drugs can be studied in parallel in children and adults once Phase I data has demonstrated the safety and pharmacokinetic properties of the drug under investigation.

"The marked increase in infections among unimmunized children during the Delta and Omicron waves of COVID-19 demonstrates that when children are not included in the original efficacy trials, they are unnecessarily put at continued risk for disease."

The FDA approved EUAs for mRNA COVID-19 vaccines for children ages 5 to 11 in October 2021, almost one year after the first EUA for adults. An EUA for children under age 5 was granted in June 2022.

THE MESSAGE OF RNA

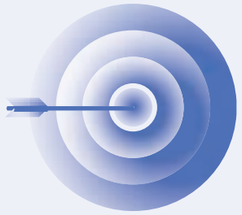
MRNA WAS DISCOVERED IN THE EARLY 1960S, a single strand of ribonucleic acid that is complementary to one of the two strands of DNA in a gene and provides the blueprint for making proteins. MRNA does not, however, change DNA (an unfounded fear voiced by some early COVID-19 vaccine opponents) and rapidly decays.

Within a decade, scientists were experimenting with using droplets of fat called liposomes to transport mRNA into cells, where the latter might induce very specific protein expression for targeted therapies.

It would take another decade or so before mRNA would be tested as a vaccine (for influenza in mice). By the 2000s, mRNA vaccines were being studied for infectious diseases ranging from rabies to Zika, though technical and logistical challenges proved daunting. Both Pfizer's and Moderna's vaccines, for example, must be stored at sub-zero temperatures to protect the fragile lipid droplets.

The global urgency of COVID-19 dramatically altered the situation. No effort could be spared. Every potential vaccine needed to be explored, no matter the challenges or costs.

RANDOMIZED CLINICAL TRIALS WORK BEST AT PREDICTING TREATMENTS BENEFITTING THE AVERAGE PATIENT, BUT MOST DISEASES AND CONDITIONS PLAY OUT IN UNIQUE WAYS IN EACH INDIVIDUAL AFFECTED. THERE IS NO SUCH THING AS AN "AVERAGE PATIENT."



New Targets

In 1999, at the bequest of officials from the National Institute of Allergy and Infectious Diseases (NIAID), Karl Hostetler, MD, a professor of medicine at UC San Diego School of Medicine, began working to convert the intravenous drug, cidofovir, to an oral version for the prevention or treatment of smallpox.

The highly infectious viral disease had been declared officially eradicated in humans in 1980, but the U.S. government and others feared smallpox might be resurrected as a weapon of bioterrorists. For the next several years, supported by grants from the NIAID and the Department of Defense, Hostetler and colleagues explored multiple prodrugs of cidofovir, eventually focusing on a lipid prodrug-type of antiviral compound called brincidofovir.

Brincidofovir blocks the synthesis of poxvirus DNA. UC San Diego licensed the compound to Chimerix, a biotech startup located in North Caroline, for further development.

Because human clinical trials were not possible, brincidofovir was one of the first drugs approved by the FDA under animal equivalence rules, which partially accounts for the long delay in approval.

Drug efficacy was established successfully in rodents, rabbits and non-human primates infected with other poxviruses, including cowpox, mousepox, rabbitpox, monkeypox and vaccinia. The drug, marketed as Tembexa, was approved for use in humans in 2021—nearly a quarter-century after Hostetler began his work.

Brincidofovir is effective against all double-stranded DNA viruses and has other potential uses, which have led to new clinical trials investigating therapeutic activity against a wide range of viral infections, including adenoviruses and herpes simplex viruses.

Messenger RNA vaccines for COVID-19 have proven their value. They are faster and cheaper to develop than traditional approaches, and their success has spurred renewed and expanded interest in using the technology for malaria, tuberculosis, hepatitis B and cystic fibrosis, plus mRNA treatments for several types of cancer.

"The COVID-19 vaccines have demonstrated that mRNA technology is safe and has the potential to be used for many other vaccines and novel therapies," said Spector.

"But they also identified a potential limitation of the technology, if it turns out that mRNA vaccines only induce short-term immunity (rather than it being a consequence of always-evolving viruses). So although mRNA technology has overcome major safety and regulatory hurdles, the long-term benefit of this technology still requires evaluation and further refinement."

N=1

CLINICAL TRIALS ARE OFTEN NOT DEFINITIVE. A drug that successfully reaches the market may prove problematic later because of unanticipated side effects. Cholesterol-reducing statins, for example, are among the most-researched and most-prescribed drugs in the world. An estimated 60 percent of Americans over the age of 65 take a statin to help prevent a heart attack or stroke. More than 200 million people take statins worldwide.

But Phase IV trials and other research have found statins can cause blood sugar abnormalities, liver damage, debilitating muscle pain or neurological issues, including memory problems and cognitive decline in some people. These adverse effects, which were considered rare or undetected in clinical trials, took years and many users to fully reveal themselves.

Conversely, noted Firestein, international clinical trials of the Alzheimer's drug aducanumab (Aduhelm) produced disappointing results and were halted in 2019. Subsequent retrospective assessments by the drugmaker suggested Aduhelm benefitted some patients. The FDA, surprisingly and controversially, approved it based on urgent need despite overwhelming opposition by its own expert advisors. The Centers for Medicare and Medicaid Services later ruled that the drug was only covered for patients in approved clinical trials.

Randomized clinical trials work best at predicting treatments benefitting the average patient, but most diseases and conditions play out in unique ways in each individual affected. There is no such thing as an "average patient."

In statistics, the symbol "n" represents the total number of individuals or observations in a sample. The "n" in the Phase III trial for Pfizer-BioNTech's COVID-19 vaccine, for example, equaled 43,661 participants.

The concept of N=1, or testing a drug on a single individual, dates back at least to 1986 and the description of a one-patient experiment in The New England Journal of Medicine. That singular trial was successful: Researchers identified a specific asthma treatment for one patient.

The trial spurred greater interest, but N=1 trials remain more anomaly than trend.

CLINICAL TRIALS IN THE FUTURE

ASK A RESEARCHER WHAT SHOULD OR COULD be changed to improve the efficacy of clinical trials, and their answers are likely to be n=many. Much has already been accomplished, such as tapping into EHRs to identify potential participants rather than leaning on doctors to find eligible patients or leveraging communications tools including social media and advertising.

Clinical trials require approval by institutional review boards (IRBs) to ensure the rights and welfare of human research subjects are protected. In recent years, there has been a shift to central IRBs, as opposed to boards at each institution, especially for multi-site studies. Central IRBs have streamlined the process by creating a single, umbrella approval for many studies.

But Firestein focuses on one particular improvement:

Is a proposed trial feasible? Are there patients that meet the entry criteria? If not, can it actually be done?

"We have wanted to do this for several years, but investigators push back, saying that it interferes with academic freedom. But a study that is not feasible because the patients don't exist doesn't help anyone." ●

7.9%

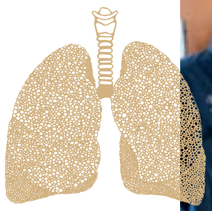
of all developmental clinical trial candidates likely to pass successfully through all phases

Source: Clinical Development Success Rates and Contributing Factors, 2011-2020, Bio, Pharma Intelligence, QLS Advisors

TRANS FORMING TRANS PLANT ATION

UC SAN DIEGO HEALTH'S
CENTER FOR TRANSPLANTATION
IS AMONG THE NATION'S BEST
IN LUNG, HEART, KIDNEY AND LIVER PROGRAMS.

BY MICHELLE BRUBAKER



Right: Stricken by COVID-19, Federico Gomez-Gil, 57, successfully underwent a double lung transplant, the first such procedure in the region and one of only a handful in the nation at the time.

ORGAN

DONATION AND TRANSPLANTATION MARKS ONE of the great advances of modern medicine, providing a second chance at life for a patient whose organs are failing or damaged beyond repair from disease or injury.

The Center for Transplantation at UC San Diego Health is a national hub of clinical expertise and research, and the region's leader in transplantation. Since 1968, the center has performed thousands of transplants under a national standard of care model.

"We provide a full spectrum of care for the entire transplantation process — from pre-transplant evaluation to post-surgical maintenance," said **Kristin Mekeel, MD**, chief of the Division of Transplant and Hepatobiliary Surgery. "Our thorough process ensures the precious gift of an organ goes to the right patient. Receiving an organ is a long-term commitment and requires a strong support system."

The transplant team includes surgeons, transplant coordinators, pharmacists, financial coordinators and nutritionists. There are also social workers and psychologists to provide emotional support and to help facilitate short- and long-term follow-up.

UC San Diego Health surgeons perform lung, heart, kidney and liver transplants — the most in the region, averaging 36 lung, 74 heart, 133 kidney and 68 liver procedures annually over the last five years.

One-year transplant patient and organ survival rates exceed national averages across all procedures, placing UC San Diego Health among the nation's best transplant centers, according to the Scientific Registry of Transplant Recipients (SRTR), which provides statistical and other analytic support for the Organ Procurement and Transplantation Network.

"The biannual SRTR report provides data analyses to transplant programs, organ procurement organizations, policymakers, transplant professionals, transplant recipients, organ donors and donor families, as well as the general public to help patients make an informed decision about where to seek an organ transplant," said **Tamra Magee**, the director of the Center for Transplantation at UC San Diego Health.

Everything begins with donors. How an organ is received, removed and transplanted has all dramatically advanced over the years, but the fundamental gift of life remains the same, as does an abiding appreciation from all involved.

For **Amy Honeycutt**, a lifesaving liver transplant she underwent in 2011 in Kansas inspired her to become a nurse and, currently, a liver transplant coordinator at UC San Diego Health.

"I am grateful every day to my donor. I can now live fully in every moment, understand my patients and their families on a deeper level and impact the lives of others," Honeycutt said.

There are not enough donors. According to the Health Resources and Services Administration, more than 40,000 transplants were performed in 2021, but almost 106,000 persons remain on the national transplant waiting list, with 17 people on the list dying each day.

Locally, 413 organs were transplanted in 2021, with almost 2,000 persons on transplant waiting lists. Eighty-seven patients died waiting for an organ in 2021, according to Lifesharing, a nonprofit involved in the organ donation process in San Diego and Imperial counties

SECOND BREATH

A TYPICAL DAY FOR ESCONDIDO RESIDENT Federico Gomez-Gil starts with making his bed, watering his garden and spending 30 minutes on his treadmill. The end of the day usually involves a walk around the block with his wife.

These simple acts represent an extraordinary achievement for the father of two and grandfather of five. "I can't believe how far I have come," said the 57-year-old Gomez-Gil. "I do not take anything for granted."

"It has been amazing to see his progress," said Guadalupe Gomez, Gomez-Gil's eldest daughter. "One day, he had all these tubes in (his body). Eventually, they were removed, and he was communicating with us. Now, we are spending quality time together and making plans for our future–something we weren't sure was possible when he was lying in that hospital bed."

In February 2021, Gomez-Gil was rushed to UC San Diego Health in critical condition, weak, feverish and struggling to breathe. He was diagnosed with COVID-19. His condition deteriorated. He developed pneumonia, permanently impairing lung function and requiring extracorporeal membrane oxygenation (ECMO), an advanced life-support technology used when a ventilator alone is insufficient.

As days passed, it became clear Gil would require a double lung transplant. A multidisciplinary team of physical therapists, respiratory therapists, pulmonologists, surgeons and nursing staff began working to get him strong enough to become a viable candidate for the transplant surgery.

On June 14, 2021, after more than 50 days on ECMO, Gomez-Gil received his new lungs during an eight-hour surgery performed by **Eugene Golts, MD**, cardiothoracic surgeon at UC San Diego Health. He was the first COVID-19 patient in the San Diego region to undergo a lung transplant. The first known double lung transplant for a COVID-19 patient in the nation had been performed just one year earlier.

"He would not have survived if he had not come to UC San Diego Health. We were able to provide him care and approaches not available at any other hospital system in San Diego," said Golts.

"Our program has grown tremendously over the past several years. Patient access, innovative treatments and a proactive, interdisciplinary care model for complex cases are what have successfully built our program with integrity and superb outcomes," said Golts.

The program, which launched in 1990, employs a variety of advanced methodologies, including a technology that improves the viability of organ donor lungs once outside of the body; the ability to safely transplant lungs from donors with hepatitis C into recipients who do not have the infection; and rare experience using bacteriophage therapy to control antibiotic-resistant lung infections.

"With improvements, such as using medications to eradicate hepatitis C in donor lungs, we are able to perform more transplants and save more lives," said **Kamyar Afshar, DO**, medical director of the lung transplant program at UC San Diego Health.

Three months after surgery, Gomez-Gil was discharged. The first thing he did after arriving home was hug his grandchildren and sit in his garden. He is on a strict medication regimen, but enjoying life. He is learning to play the guitar.

Above: Kristin Mekeel, MD, PhD, in the operating room. UC San Diego Health surgeons perform an average of 36 lung, 74 heart, 133 kidney and 68 liver transplant procedures each year, the most in the region.

HEART-TO-HEART

THE AMERICAN HEART ASSOCIATION ESTIMATES 6 million Americans are living with heart failure, with approximately 60,000 suffering end-stage disease when conventional therapies no longer work. For these persons, a heart transplant becomes the only lifesaving option.

With a national shortage of donated organs, patients requiring a heart transplant can wait months, even years, for an organ. With the passage of time comes the increasing risk of their passing.

"It often feels like we are racing against the clock, trying our best to keep severely sick people alive, doing whatever possible until we find a suitable organ," said **Eric Adler, MD**, cardiologist and medical director of cardiac transplant and mechanical circulatory support at UC San Diego Health.

"OUR THOROUGH PROCESS ENSURES THE **PRECIOUS GIFT** OF AN ORGAN GOES TO THE RIGHT PATIENT. RECEIVING AN ORGAN IS A LONG-TERM COMMITMENT AND REQUIRES A STRONG SUPPORT SYSTEM."

KRISTIN MEKEEL, MD, PHD

UC San Diego Health's heart transplant program debuted in 1989; and performed its first heart transplant in 1990. Approximately 500 heart transplants have since been performed.

In 2011, Sulpizio Cardiovascular Center at UC San Diego Health opened its doors, offering patients access to leading diagnostics, novel treatments and several clinical trials unavailable elsewhere in the region.

Led by **Victor Pretorius, MBchB**, surgical director of cardiac transplant and mechanical circulatory support at UC San Diego Health, and Adler, the heart transplant program has become the largest in San Diego and the second largest in California. It ranks among the nation's top-performing transplant centers.

"We are determined to treat heart failure cases in our region and beyond. We offer the most advanced transplant services combined with a personal connection to our patients," said Pretorius.

In 2020, UC San Diego Health was the first hospital on the West Coast to perform heart transplant surgery from a donor after circulatory death, or DCD, using a new portable organ care system. The successful surgery was part of a national interventional clinical trial that could increase organ donation by an estimated 20-30 percent, resulting in shorter wait times for patients in need of a new heart.

DCD involves retrieving organs from hospitalized donors who have died because their heart has stopped, either naturally or because life support has been discontinued. In such cases, with prior consent, surgeons remove the organ — within 30 minutes — and connect it to a machine that perfuses the heart with warm blood, reviving and keeping the organ beating and functional for assessment and possible transplantation. The warm perfusion system can potentially keep the organ viable for longer periods than traditional cold storage, allowing for transportation of organs over much longer distances.

"When it comes to how organs are procured and preserved from donors, this machine is changing the paradigm for heart transplants," said Pretorius. "Not only will this increase the number of hearts available for those in need but it can also optimize the timing of the transplant operation and utilization of operating room resources."

"WE OFFER THE MOST ADVANCED TRANSPLANT SERVICES COMBINED WITH A **PERSONAL CONNECTION** TO OUR PATIENTS."

VICTOR PRETORIUS, MBCHB

Ongoing research in cardiac transplant includes the evaluation of new drugs to prevent rejection that are more effective with fewer adverse effects, as well as new mechanical devices that can assist the heart.

"Over the last decade, we have seen remarkable growth in the heart transplant program, with high volumes, outstanding outcomes and leading-edge research," said Adler. "Most importantly, we have given a renewed life to countless San Diegans, none of which would be possible without an extraordinary team and the generous organ donors."

LIVING, PAIRED, EXCHANGE OR VOUCHER

THE KIDNEY TRANSPLANT PROGRAM AT UC SAN Diego Health was the first of its type in the San Diego region, starting in 1968. It is also the largest: Nearly 3,200 transplants have been performed.

The program offers different transplant approaches:

- A deceased kidney donation from a donor who has been diagnosed as "brain dead" but whose other organs remain functional.
- A donor kidney from a living donor, such as a family member or friend. In California, kidney transplant candidates with blood type O sometimes wait up to 10 years for a kidney from a deceased donor. Living donations help reduce the risks of waiting.
- A paired kidney transplant, which allows donors who are not blood- or tissue-compatible with their recipient to "exchange" their kidney with a donor who is compatible.

Kidney vouchers allow donors to donate a kidney many years before their intended recipient may need one. In 2014, UC San Diego Health was the first San Diego transplant program to implement the program.

"It is such an honor to do what I do for a living and give patients a better quality of life," said Mekeel. "I also get to witness family members donating to loved ones and strangers donating to patients, giving life through the selfless act."

UC San Diego Health works closely with the National Kidney Registry, which provides access to paired, chain and voucher donations from a national patient list. This program offers patients with living donors who are not a match an opportunity to still receive a living donor transplant within a short time frame.

"Living donation offers kidney transplant patients the best option for a timely transplant with a long life span. Patients do not have to wait on a list and are immediately off dialysis after the transplant," said Mekeel.

"With the national kidney pairs and chain donations, any patient who has an available living donor can get a transplant. These advancements in kidney donation have increased access to transplant for many transplant recipients, as well as improving outcomes for those patients."

UC San Diego Health is also among the few programs in Southern California where patients can receive kidney auto-transplants, a procedure in which surgeons remove a kidney, repair a medical problem or defect, and then return the organ to the body.

This procedure is useful in treating patients with anatomic diseases that affect kidney function or quality of life, such as nutcracker syndrome, a rare vein compression disorder that squeezes the left renal vein.

SHARE AND SHARE A LIFE

One organ donation can save eight lives. One donor can help up to 75 others through gifts of eye, bone, skin and other tissues.

UC San Diego Health works closely with Lifesharing, founded in 1973 to support UC San Diego Medical Center's burn center and kidney transplant program. Lifesharing now serves all hospitals as the federally designated organ procurement organization for San Diego and Imperial counties. For more information, visit lifesharing.org.

UC San Diego Health and Sharp HealthCare conduct a joint blood and marrow transplantation program, the largest in San Diego and among the largest in California.

In 2019, UC San Diego Health and Lifesharing performed their first honor walk, a tribute to donors that allows loved ones and medical teams to accompany patients to the operating room before an organ donation is made, often with staff and others lining the hallways. An original chime, created by a UC San Diego Health nurse, plays throughout the hospital to signal an honor walk is occurring.

40,000+
Transplants performed nationally in 2021

106,000
People on national transplant wait lists

17
People who die each day while on wait lists

413
Transplants performed in the San Diego region in 2021

2,000
People on local wait lists

87
People on local wait lists who died in 2021

2019 HONOR WALK

Medical staff and San Diego Fire-Rescue Department members line the hallway at UC San Diego Medical Center as Robin Cervantes is moved to the operating room. Cervantes, a 54-year-old fire captain, was gravely and irreparably injured in an off-duty accident. His organ donation became the first honor walk in 2019.

Sources: U.S. Health Resources and Services Administration, Lifesharing of San Diego and Imperial counties

LIVER AND LET LIVE

HUSBAND AND FATHER OF FOUR, ANDY PATRIDGE, 53, was diagnosed in 2018 with primary sclerosing cholangitis , a disease that can lead to inflammation and scarring within the bile ducts, eventually resulting in serious liver damage.

"I was in total shock when I learned I was in late-stage liver disease," said Patridge.

After moving to San Diego, Patridge transferred his care to UC San Diego Health where it was determined he needed a liver transplant.

UC San Diego Health's live liver donation program is unique in San Diego County and one of only two in Southern California. A living donor liver transplant involves surgically removing a portion of liver from a healthy person and transplanting it into a patient whose liver is failing. Regeneration of the liver in both the donor and recipient begins immediately, with the organs returning to 80 percent of their original size within six weeks and up to 90 percent after one year.

Patridge's friends and family members were all tested as possible donors. His brother, Mike, was a match, not just in blood type, but also in the actual size of the organ. Standing at 6 feet, 5 inches, Andy needed a large liver.

"I'm 6-foot-7, so I knew I would be a strong candidate," said Mike, 51, who flew to San Diego from England to go through the testing process.

On March 2, 2022, the brothers prepared for the surgery.

"I vividly remember looking at us in our surgical caps and gowns waiting to be wheeled into the operating room. It was nerve-wracking to know what was about to happen," said Andy.

The transplant went well all around. "With live liver donation, we can control the timing of transplant, which means the recipient can be transplanted much sooner and before they become severely ill. This allows patients to better manage the demanding process of liver transplantation," said **Justin Parekh, MD**, transplant and hepatobiliary surgeon at UC San Diego Health.

The liver transplant program at UC San Diego Health performed 82 transplants in 2021.

Nationally, there are more than 12,000 people in need of a liver transplant, including more than 2,300 in California.

"AS THE REGION'S ONLY ACADEMIC MEDICAL CENTER, WE ARE ABLE TO OFFER PATIENTS THE MOST ADVANCED TREATMENT OPTIONS THROUGH CLINICAL TRIALS."

SAIMA ASLAM, MBBS

In September 2020, UC San Diego Health became the first health care system in Southern California to transplant a liver from a donor with human immunodeficiency virus (HIV) into an HIV-positive recipient. The successful surgery was part of a national clinical trial that could lead to more lifesaving options and less time on the transplant wait lists for HIV-positive patients. To date, five patients in the national trial have undergone liver transplants.

UC San Diego Health is participating in three national clinical trials supported by the HIV Organ Policy Equity (HOPE) Act, passed in 2013. The HOPE Act permits transplant teams in the United States with an approved research protocol to transplant organs from donors with HIV to qualified recipients with HIV and end-stage organ failure.

"As the region's only academic medical center, we are able to offer patients the most advanced treatment options through clinical trials," said **Saima Aslam, MBBS**, director of the solid organ transplant infectious diseases service at UC San Diego Health and a trial principal investigator.

"We want evidence-based results to better understand the outcomes of using an HIV-positive organ versus an HIV-negative organ in a patient infected with HIV. Do they have the same short- and long-term outcomes?"

For patients with hepatocellular carcinoma (HCC), one of the most common predictors for liver transplant, quicker transplant evaluation increases the probability of a successful procedure before the tumor spreads.

"We recognized the need to evaluate this population quickly and implemented an expedited evaluation protocol that decreased their evaluation time by 80 percent," said **Veeral Ajmera, MD**, medical director of liver transplantation at UC San Diego Health.

A recent study by UC San Diego Health physician-scientists found that patients with advanced HCC who were treated with immunotherapy can progress to curative liver transplant in select situations. Historically, this type of treatment precluded liver transplant.

"We are excited to be part of these groundbreaking efforts, which are helping to move science forward," said **Gabriel Schnickel, MD**, surgical director of liver transplantation at UC San Diego Health.

The Patridge brothers are continuing to recover and are back to their daily activities.

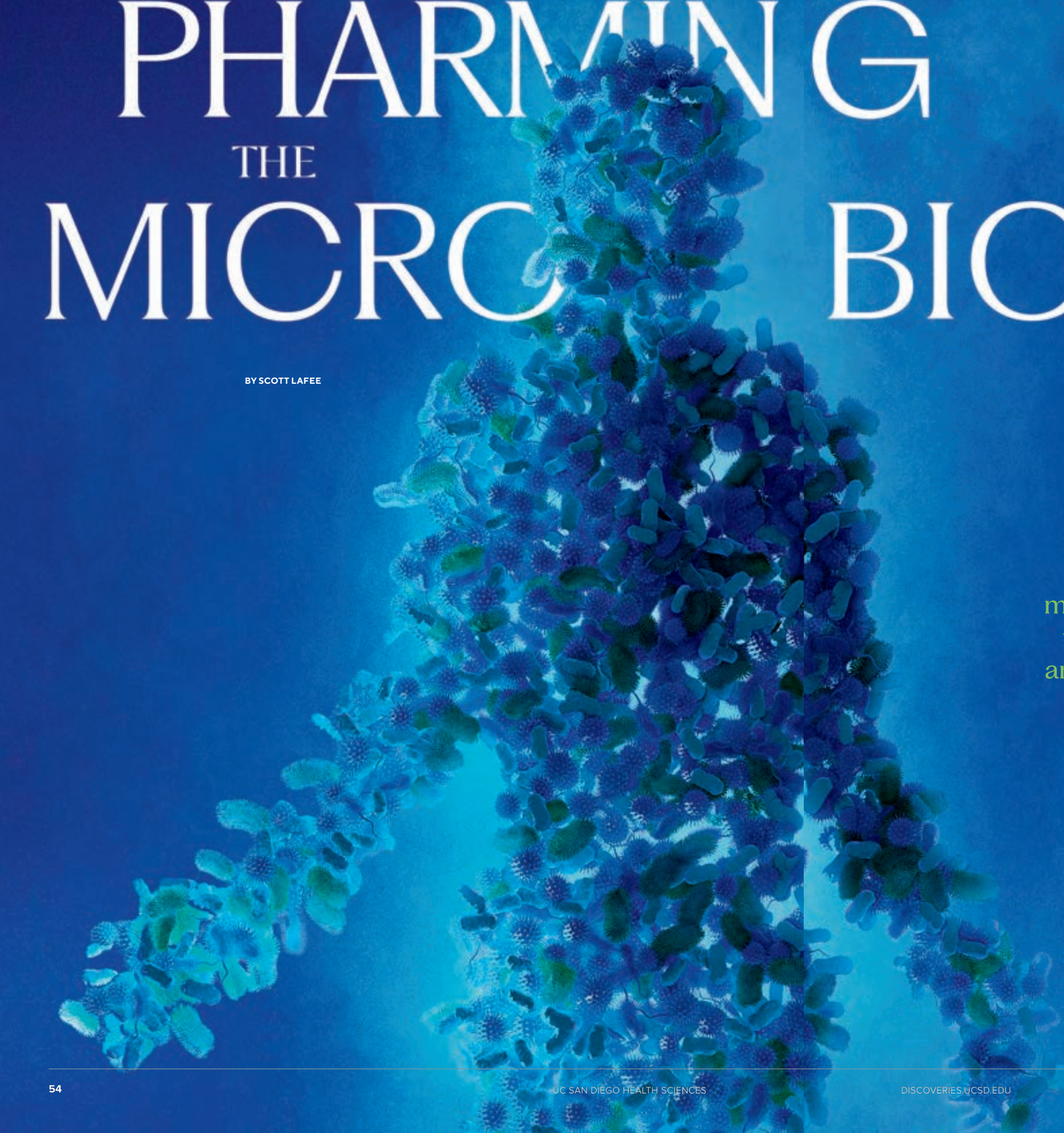
Andy recently went on a hike at an elevation of 6,000 feet.

"I didn't realize how sick I was until after the transplant. What Mike did for me was a true gift." ●

Right: Mike Patridge (center) donated a portion of his liver to his brother Andy (third from left) as part of the live liver donation program at UC San Diego Health, one of only two in Southern California.

PHARMING THE MICROBIOME

BY SCOTT LAFEE



The collective communities of microorganisms within each of us alter the way drugs work, for good and ill, and may be a source of new medicines themselves if we can parse their multitudinous mysteries.

AT THE TURN OF THE 20TH CENTURY, GERMAN PHYSICIAN-SCIENTIST PAUL EHRLICH WAS busily transforming medicine: finding a cure for syphilis and a way to stain bacteria for identification purposes, providing a name for the concept of chemotherapy and popularizing the notion of a therapeutic "magic bullet."

EHRLICH'S CONTRIBUTIONS STILL RESONATE,

PERHAPS MOST NOTABLY THE IDEA THAT IT IS POSSI-ble to design and dispense pharmacological compounds that will target and kill specific types of unwanted cells, from pathogens to cancer, without harming healthy cells. A magic bullet, so to speak.

But new scientific disciplines, such as genomics, proteomics, metabolomics and microbiomics, have revealed that life is far more complicated than Ehrlich and others might have imagined, and so, too, the conditions that ail us. Modern medicine needs a lot more bullets.

It is a myth that bacteria and other microbes in our bodies outnumber our own cells 10 to 1. Nonetheless, the human body is extraordinarily bounteous in microbial life, consisting of approximately 30 trillion "human" cells and another 40 trillion or so nonhuman microbial cells. The typical person is more microbe than human, and in their entirety, these microorganisms account for an estimated 2 to 6 pounds of average human body weight.

Genetically, the numbers are even more dramatic. The human genome consists of roughly 20,000 genes; the human microbiome expresses 2 to 20 million genes. Even within what is usually considered the "human" genome, 8 percent of human DNA consists of viral remnants; another 40 percent may have viral origins.

Our microorganisms conduct the business of our lives. They digest food; maintain pH levels in saliva, bile, gastric acid and tears; remove dead cells so that live ones can take their place; and colonize every available nook and cranny, inside and out. Our mouths harbor more than 700 species of bacteria and our skin perhaps 1,000 species, plus assorted viruses, fungi, yeast and other forms of life.

Resident microbes determine biological function. In 2020, **Pieter Dorrestein, PhD**, professor and director of the Collaborative Mass Spectrometry Innovation Center in the Skaggs School of Pharmacy and Pharmaceutical Sciences at UC San Diego, and colleagues published a *Nature* paper reporting that as much as 70 percent of a mouse's gut chemistry is determined by its gut microbiome. Even in distant organs, such as the uterus or the brain, it was estimated that approximately 20 percent of resident molecules are influenced by gut microbes.

"We hear a lot about how our own human genes influence our health and behaviors, so it may come as a shock to think that we could have molecules in the body that look and act the way they do not because of our genes, but because of another living organism," Dorrestein said.

From the moment of birth — indeed from the manner of birth — our microbiomes change with exposure to the world and people. Microbiota are altered by what we eat, where we live and even how we sleep. By age 3, each human being is a unique collection of microbial communities — distinct sites on our bodies as different in terms of their microscopic residents as San Diego soil is from San Diego River water.

"While we are only approximately 0.1 percent genetically different within our human genome, we can be up to 90 percent different in terms of our microbial genomes," observed **Rob Knight, PhD**, professor and director of the Center for Microbiome Innovation in the Jacobs School of Engineering, with colleagues, in the 2019 edition of *Concepts and Principles of Pharmacology*.

For the most part and most of the time, human microbiota live in harmony with their hosts. Nearly everyone carries pathogens — microorganisms known to cause illness — but in healthy individuals, these pathogens tend to coexist harmlessly.

It is a dazzlingly complicated interspecies relationship. Apart from the sheer number of players involved is the even greater number of interactions between them, which includes the trillions of metabolites (molecules generated by the process of metabolism) created by biochemical reactions within cells. By some estimates, this endless production works out to 37,000 billion billion (37 followed by 21 zeros) chemical reactions per second in the human body.

> "While we are only approximately 0.1 percent genetically different within our human genome, we can be up to 90 percent different in terms of our microbial genomes."
>
> **ROB KNIGHT, PHD**

Microbiome numbers

700+
Estimated number of bacterial species living in our mouths[1]

1,000+
Estimated number of bacterial species living on our skin[2]

20,000
Human genes[3]

2–20M
Microbial genes in human microbiome[3]

2–6 lbs
Weight of microbes in average human body[4]

1. Priya Nimish Deo et al. "Oral microbiome: Unveiling the fundamentals." *Journal of Oral and Maxillofacial Pathology*. Jan-April 2019.
2. "Your Body Is a Wonderland ... of Bacteria." *Science*. May 28, 2009.
3. Ron Sender et al. "Are We Really Vastly Outnumbered?" *Cell*. January 28, 2016.
4. National Institutes of Health Human Microbiome Project

In recent years, much effort has been expended to understand better how the almost unlimited elements of the microbiome and their work products cause disease. Why, for example, does a previously unthreatening pathogen turn deadly? How do individual microbiomes keep people healthy, even as some necessary medications or treatments do quite the opposite? Can we find new magic bullets in the microbiome?

Answers are coming. Doctors now know that the microbiome plays an important role in whether a patient will respond to some forms of chemotherapy for cancer or suffer adverse effects. Irinotecan is a type of chemotherapy for treating colon cancer, but when metabolized by some species of gastrointestinal bacteria, it causes severe diarrhea. A better understanding of an individual's microbiome — and more precisely what is residing in the gut — would help doctors stratify which patients are most likely to benefit from a drug such as irinotecan and which will likely be worse off.

There are increasing efforts to leverage the microbiome to more directly restore or promote health. The most notable case, perhaps is fecal microbiota transplantation (FMT) to treat infections of *Clostriodioides difficile*, a bacterium that causes severe diarrhea and inflammation of the colon and is resistant to most antibiotics.

FMT is celebrated as one of the first and most high-profile examples of successful bacteriotherapy. It involves the transfer of stool from a healthy donor into the gastrointestinal tract of a patient with recurrent *C. difficile* colitis. The intent is to replenish and restore a healthy bacterial balance. "It's a key example to date of a clinical application for commensal microbes as live biotherapeutic agents," wrote Knight and colleagues.

FMT is now considered a standard of care for *C. difficile* colitis. It has an estimated cure rate of 85 to 95 percent, according to published data, though treatment may require multiple applications.

Other bacteriotherapy efforts are more literally more superficial, but equally encouraging. **Richard Gallo, MD, PhD**, Distinguished Professor and founding chair of the Department of Dermatology at UC San Diego School of Medicine, and colleagues are developing a topical treatment derived from skin bacteria for atopic dermatitis, the most common form of eczema. Atopic dermatitis causes red and itchy skin, and afflicts nearly 10 million children and more than 17 million adults in the U.S.

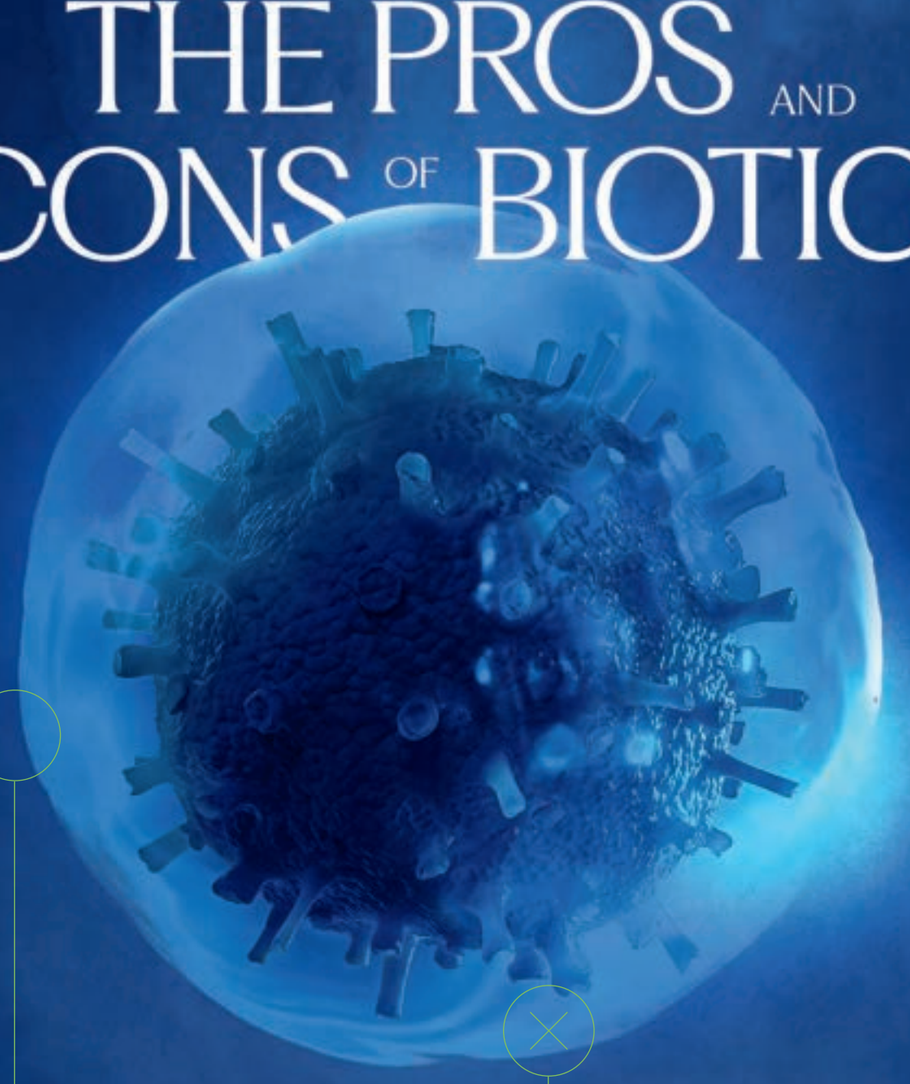
In February 2022, Gallo and colleagues published a study describing a universal strain of bacteria derived from healthy human skin that, when applied in a lotion to the skin of patients with atopic dermatitis, resulted in the introduced harmless bacteria inhibiting the growth of *Staphylococcus aureus*, a pathogenic bacterium that aggravates skin conditions, including eczema. Clinical trials are ongoing.

PIETER DORRESTEIN, PHD

RICHARD GALLO, MD, PHD

ROB KNIGHT, PHD

THE PROS AND CONS OF BIOTICS



When consumed or applied to the skin, probiotics are intended to help restore or improve microbiome balance or counter the adverse effects of medications or treatments, such as antibiotics or cancer chemotherapy.

The most common therapeutic bacteria used belong to the groups *Lactobacillus* and *Bifidobacterium*, which both occur naturally in and on the human body. They are also found in yogurt and other fermented foods, dietary supplements and beauty products.

A 2012 national survey reported that approximately 4 million U.S. adults (1.6 percent) said they used probiotics or prebiotics in the previous 30 days, quadrupling the number from 2007.

Whether probiotics are effective remains a matter of investigation. Probiotics have shown promise for a variety of conditions, such as preventing of antibiotic-associated diarrhea, necrotizing enterocolitis and sepsis in premature infants and treating of infant colic and periodontal disease.

But there are limitations. Much like drugs, specific probiotic strains work for specific indications, but not other indications. Tylenol, for example, won't help a runny nose. And probiotics do not improve health above baseline, said Knight.

"They definitely won't make you feel extra good if you take them when you're feeling generally fine."

Sometimes, probiotics don't work. Studies of other maladies, such as allergies, asthma, acne, upper respiratory infections and urinary tract infections, have found little to no benefit, were inconclusive or were deemed unpersuasive.

Like other dietary supplements, probiotics are not regulated by the FDA. They do not need to be proven safe or effective to be marketed, and so there are very few empirical studies that support their use for specific ailments or in generally healthy people. They are presumed safe, but may pose greater health risks to persons with severe illnesses, underlying medical issues or compromised immune systems.

THE HUMAN GASTROINTESTINAL TRACT IS THE MOST-STUDIED OF MICROBIOMES.

IT IS RICH IN DIVERSITY AND ABUNDANCE — AN estimated 1 billion bacteria per milliliter of content representing up to 1,000 possible species in the colon alone — and strongly linked to both health and disease.

One of the first discoveries linking microbiota to a human ailment involved inflammatory bowel disease (IBD). The causes of IBD aren't fully understood, but it's clear that the chronic condition is moderated by gut microbiota: too much or too little. Too many of the "wrong" bacterial species and not enough of the "right" all play a part, influenced by factors such as genetics, diet, drugs and stress.

Antibiotics are celebrated as a marvel of modern medicine. They represent one of the most successful forms of chemotherapy in history, effectively treating a vast array of diseases in the 20th century and dramatically extending the human lifespan.

But apart from their diminishing returns due to evolving antimicrobial resistance, broad-spectrum antibiotics pose peril to the human microbiome, killing not just targeted pathogens, but also harmless and beneficial microbes. Not only does prolonged or indiscriminate use of antibiotics reduce overall microbial diversity (not a good thing), it opens the door and space for opportunistic pathogens such as *C. difficile* and may lead to greater risk of autoimmune and metabolic diseases, such as diabetes, asthma and allergies.

The gut microbiome plays a role, too, in cardiovascular disease by altering how nutrients are broken down. In some cases, it appears, these changes lead to dysregulated metabolic aspects of cholesterol and elevated heart disease risk.

And then there's the "gut-brain axis," a two-way signaling network between the gastrointestinal tract and the central nervous system in which gut microbiota are major players. Studies have found that alterations in gut microbiota are associated with anxiety and depression because their signaling molecules act as sensory information transmitted to the brain. Neuroimaging suggests that an abundance of certain bacterial taxa in the gut, and its resulting byproducts, may influence neurological disease.

A 2020 study by **Olivier George, PhD**, professor of psychiatry at UC San Diego School of Medicine, and colleagues reported that antibiotic treatment and depleted gut microbiota in rats dramatically changed how their brains functioned during opioid addiction and withdrawal.

"The most surprising thing was that the rats all seemed the same on the surface," said George when the study was published in *eNeuro*. "There weren't any major changes in the pain-relieving effect of opioids, or symptoms of withdrawal or other behavior between the rats with and without gut microbes, but in the end, it became clear that, at least in rats, gut microbes alter the way the brain responds to drugs."

Less is known about other non-antibiotic drug classes, though there are increasing reports that other medications also alter the composition of the gut microbiome to good and bad effect.

Metformin, for example, is widely prescribed to treat diabetes, but its impact on the gut microbiome is felt too. Proton pump inhibitors, commonly used to reduce stomach acid and heartburn, also reduce and change gut microbiome diversity, elevating the risk of *C. difficile* infection.

Conversely, gliptins, a class of antidiabetic agents used to control blood sugar levels, have been found in mouse studies to inhibit some pathogenic types of gut bacteria, improving microbiome health.

The efficacy of any drug largely depends upon how well it is metabolized by the body or by targeted parts of the body. A medication that works for one person doesn't necessarily work for another with the "same" condition.

MICROBIOME GLOSSARY

Dysbiosis
A state of microbiome imbalance, especially of the gut, that increases the chance of disease or ill health.

Probiotics
Live microorganisms intended to produce health benefits when consumed or applied to the body.

Prebiotics
Nondigestible food components, such as plant fibers, that serve as a food source for gut microflora, which metabolize and ferment the prebiotics to survive and, in the process, create byproducts beneficial to the host.

Synbiotics
Combining probiotics and prebiotics to create synergistic benefits.

METABOLISM IS HIGHLY VARIABLE AMONG INDIVIDUALS,

INFLUENCED TO SOME DEGREE BY GENETIC variation, which again largely means the particular mix of microorganisms living within them.

For example, microbes help determine how drugs degrade in the human body. Some contribute to the activation of medications, such as sulfasalazine, a rheumatoid arthritis drug that requires a bacterial enzyme to help turn it on.

Other microorganisms inactivate drugs, reducing their bioavailability and usefulness. Patients with cardiac arrhythmia and heart failure may be prescribed digoxin, a therapeutic that must be maintained at specific levels in the bloodstream to be effective. However, certain bacterial strains metabolize digoxin, rendering it inactive and the patients at greater risk if levels drop.

The microbiome can also limit the therapeutic benefit of drugs by simply using the same metabolic pathways. Some patients are at higher risk of liver damage caused by acetaminophen, the active ingredient in many pain relievers, because their gut microbiota have reduced the ability to metabolize it elsewhere.

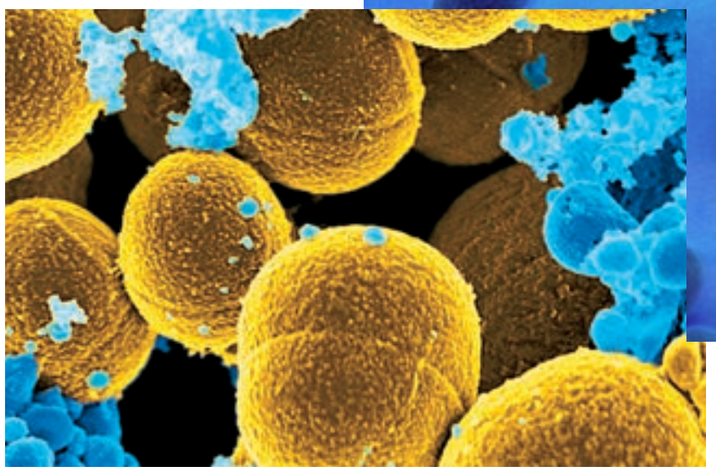
Our microbial partners offer a source of new drugs. Nearly half of all FDA-approved human pharmaceuticals originate from natural sources. Aspirin famously evolved from a compound found in the bark and leaves of the willow tree; penicillin, lovastatin and taxol also derive from terrestrial plants and microbes.

But more than two-thirds of the planet is covered by ocean, said **Bradley Moore, PhD**, Distinguished Professor at Skaggs School of Pharmacy and Pharmaceutical Sciences and Scripps Institution of Oceanography, making it a vast and rich repository of marine-derived pharmacopoeia, especially microbial. Marine microorganisms comprise an estimated 70 to 90 percent of the oceans' biomass. A single liter of seawater may contain 1 billion bacteria and 10 billion viruses.

Moore and colleagues at the Center for Marine Biotechnology and Biomedicine at Scripps Institution of Oceanography are investigating scores of aquatic sources, from algae to sea slugs to deep-sea microbes, for new medications.

Two cancer drug candidates currently in Phase III clinical trials — marizomib and plinabulin — are derived from marine bacteria and fungi discovered and developed by **William Fenical, PhD**, and **Paul Jensen, PhD**, both at Scripps.

"These examples showcase the remarkable promise of marine microbes and their distinctive chemical language in providing new opportunities to treat disease," said Moore, who, along with colleagues, has reported promising marine-derived pharmaceuticals from organisms ranging from cyanobacteria and sponges to soft corals, all of which may have therapeutic applications as antibiotics, antivirals or anticancer agents.



CHRISTINE TARA-PETERSON, PHD

Other scientists are looking within for remedies. New abilities to mine the human microbiome are allowing researchers to identify natural microbial products analogous to known drugs. Like microbes everywhere, human microbiota must compete for finite space and resources and so have evolved a variety of tools to survive, including "quorum quenching" molecules that disrupt signaling and growth of other microbes. These molecules could be exploited to treat biofilm infections—colonies of mixed or single bacterial types that are particularly resistant to antibiotics and other threats.

Beneficial bacteria known as probiotics and the foods they eat (prebiotics) could be tapped as well, and there are a number of efforts underway to use them to treat conditions from oral and allergic diseases to major depressive disorder.

Left: a colorized micrograph of *Staphylococcus aureus* (yellow), a bacterial pathogen that is the leading cause of skin and soft tissue infections. Above: *Escherichia coli* bacteria are generally harmless residents, but some strains can cause intestinal distress or worse.

In a study published in the *Journal of Integrative and Complementary Medicine*, for example, **Christine Tara Peterson, PhD**, assistant project scientist in the Department of Family Medicine at UC San Diego School of Medicine's Center of Excellence for Research and Training in Integrative Health, and colleagues described the prebiotic potential of herbal medicines.

They found that three herbal medicines commonly used in Ayurveda for the treatment of gastrointestinal health and disease alter the growth and abundance of specific bacterial species, which may improve colon function, reduce inflammation and protect against opportunistic pathogens.

"Medicinal herbs are chemically complex, much more than the word 'herb' may commonly conjure," said Peterson. "Ayurvedic herbs potentially yield a host of medicinal properties with far-reaching effects on multiple targets and body systems.

"I am working within the scope of a new emerging model whereby herbal medicine and product development move beyond a single target or traditional pharmaceutical molecule approach to an expanded view that includes the microbiota-mediated therapeutic effects of herbal medicines and allows for the potential of multiple molecules of interest (both herb-derived and microbe-generated) to better explore complex, multi-target and multisystem responses to traditional herbal medicine."

Finally, it may be possible to engineer existing commensal microorganisms to perform better or differently. Some strains of *Escherichia coli* bacteria are notorious for causing intestinal distress, urinary tract infections and, sometimes, life-threatening kidney failure, but most *E. coli* species reside naturally and harmlessly in the gut where they, at the very least, prevent colonization of the intestines by more dangerous microbes.

Researchers have engineered commensal *E. coli* to sense and disperse biofilms created by *Pseudomonas aeruginosa*, a pathogenic bacterium that causes serious disease, including pneumonia and septic shock.

E. coli bacteria have also been genetically modified to produce phenylalanine-metabolizing molecules in animal models of phenylketonuria, a rare inherited disorder in which accumulation of the amino acid phenylalanine can lead, without treatment, to severe brain damage.

Last year, the National Institutes of Health launched a new consortium called Nutrition for Precision Health. Part of that effort includes a Microbiome and Metagenomics Center at UC San Diego to analyze the microbiomes found in stool samples of study participants, based on the idea that what we eat affects our gut microbiomes, which, in turn, affects our overall health.

"Bringing this expertise and technology to bear on the incredibly challenging problem of nutrition and health will enable a whole new level of precision in answering the age-old question of 'What should I eat today'?'" said Knight. "We are just starting to understand how the microbiome can answer this with a surprising level of individual detail, not just broad-strokes generalizations for the whole population." ●

SMARTLY DONE

BY NICOLE MLYNARYK

Artificial intelligence is on its way to transforming how we understand and treat disease.

WHEN A STEM CELL

TRANSPLANT PATIENT ARRIVED AT UC SAN DIEGO

Health with sudden chest pain and difficulty breathing, doctors raced to find a diagnosis. A CT scan revealed pockets of air surrounding his heart and filling the space between his lungs, but it required analysis from a radiologist to connect the dots and solve the medical mystery.

Albert Hsiao, MD, PhD, reviews hundreds of clinical images a day — CT scans, X-rays, MRIs — using his keenly trained eye to identify signs of disease. But unlike standard radiologists, Hsiao is also equipped with an additional tool: artificial intelligence (AI).

Many have hinted at AI's great potential to enhance practices across research and medicine, with applications spanning everything from radiology and surgery to disease modeling and drug discovery, and even patient safety and cybersecurity. But physicians and scientists are still working to translate that potential into real-world use, with UC San Diego faculty among those leading the charge.

As an associate professor of radiology at UC San Diego School of Medicine and associate director of the Center for Translational Imaging and Precision Medicine at UC San Diego Health, Hsiao leads a prolific research team that specializes in developing AI tools. Their sophisticated software programs augment analyses of all sorts of clinical images.

On this day, he happened to be equipped with a new algorithm for measuring air trapping in the lungs. Such air trapping is invisible to most radiologists, so when the patient received a routine CT scan two months prior, the images appeared normal. But when Hsiao reanalyzed them with this new tool, the AI was able to see something physicians could not.

The machine learning algorithm was trained to calculate the amount of air trapping in the lungs and highlight any signs of it in the scan in blue. In the dimly lit radiology room, two almost entirely blue lungs appeared on Hsiao's screen.

"IT WAS THE MOST

AIR TRAPPING I'D EVER SEEN," SAID HSIAO. The patient had developed spontaneous pneumomediastinum, a rare side effect of his immune response to the stem cell transplant. So much air had been trapped in his lungs that it eventually had to escape into his chest cavity, producing the symptoms that brought him back to the hospital.

The patient's condition was successfully treated, the utility of the AI algorithm clearly shown.

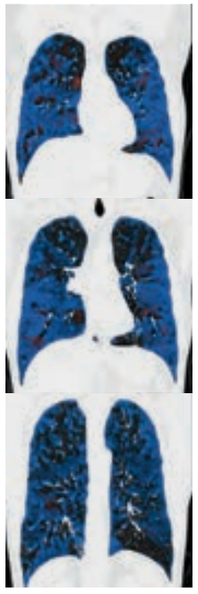
"If we hadn't gone back and looked at the lungs this way, we'd have no explanation for how this happened," said Hsiao. UC San Diego Health now uses this technology to screen for air trapping in stem cell transplant patients.

This is one example of the vast array of AI tools Hsiao and his colleagues have been working on. In each project, the researchers feed clinical scans into a machine and give it a specific task to do, such as calculating air trapping. Using deep learning methods, an AI algorithm reviews the images, looking for any structures and patterns in the data that it can use to complete the task.

"An expert radiologist spends years and years reviewing clinical images, training their brain to identify these subtle visual signs of disease. An artificial neural network can learn them in hours."

Hsiao's team has developed tools to detect early signs of pneumonia in X-rays, which became critical to UC San Diego Health's triage of COVID-19 patients. In another study, they had a machine review thousands of images of heart disease patients, looking to see if there were any common patterns in their cardiac muscle motion. The algorithm identified three distinct groups in the population: one with typical muscle motion, another with a poorly contracting left ventricle and a third requiring pulmonary valve replacement.

"These are patterns that can only be found through painstaking, systematic review of a huge number of clinical scans," said Hsiao. "Even the best physicians seeing lots of patients aren't going to be able to spot these things on their own."



An AI tool reveals air trapping (blue) in patients' lungs.

But Hsiao isn't worried about machines taking his job anytime soon. He sees this collection of algorithms as "another pair of eyes" helping him do his job better and more efficiently.

"A radiologist should be a detective," he said. "If you're in a rush to read 400 X-rays just to say if something appears in the image or not, you haven't actually solved the problem of why the patient is coming for help. If I can get a computer to read those X-rays for me, I could spend that time focusing on patients that really need my attention, or building the next AI tool."

BRIDGING BENCH AND BEDSIDE

ANOTHER APPLICATION OF AI TOOLS IS TAKING off not in the clinic, but in the lab. **Pradipta Ghosh, MD**, professor of cellular and molecular medicine at UC San Diego School of Medicine, is one of several researchers advancing the use of AI to develop better models of disease.

Over her years of clinical practice, Ghosh became disillusioned with how little the field could truly explain the origins of many diseases, and how difficult that made it to develop effective treatments.

The classic way to define a disease is through its symptoms. Based on observations in the clinic, the physician's mind does exactly what an algorithm would do: it looks for patterns and tries to identify the clearest difference between a sick person and a healthy one. The problem, Ghosh said, is that these overt symptoms usually reflect later stages of disease.

"When we try to define a disease or develop cures for it based on overt symptoms, we often fail, and spend a lot of time and money in the process," said Ghosh. "In many cases, the most obvious symptoms are red herrings that distract us from the real issue, which is often many biological steps earlier."

Examples include the significance of amyloid plaques in the progression of Alzheimer's disease, or the role of inflammation and fibrosis in inflammatory bowel disease. Many clinical trials testing drugs that target these symptoms have not been successful, disappointing physicians and patients in the process.

Fortunately, scientists now have much more data to learn from than even just a few years ago and better learning machines. Ghosh's team is looking to trace disease not through clinical symptoms alone, but through gene expression patterns and the cellular processes to which they correspond.

To do this, they first measure levels of gene expression in models of health and disease, which can take the form of patient tissue samples, human cell lines or lab-grown organoids (See P.68.) They then use AI algorithms to identify differences between them.

To develop these tools, Ghosh has teamed up with **Debashis Sahoo, PhD**, associate professor in the departments of Computer Science, Engineering and Pediatrics at UC San Diego. Though trained in different fields, Ghosh said she and Sahoo share a similar philosophy on the cell.

"A lot of complex biology can be boiled down to a few fundamental processes," she said. Ghosh and Sahoo see cells as little machines, constantly integrating a slew of input signals and coming up with a molecular response. "But there are really only a few core responses a cell can choose from: to divide or not divide, to live or to die, and so on."

In their view, each disease comes down to some moment when the cells reach one of these molecular checkpoints and, for some reason, make the "wrong" decision. This event then leads to a cascade of downstream effects that eventually manifests as disease.

"Our goal is to develop algorithms that can look at the data and identify these critical checkpoints along the progression of a disease, and find which genes or proteins are involved at each one," said Ghosh. By doing this, researchers will be able to identify what stage of disease a patient is at based on their current gene expression patterns, and suggest a drug that targets the genes most influential at that stage.

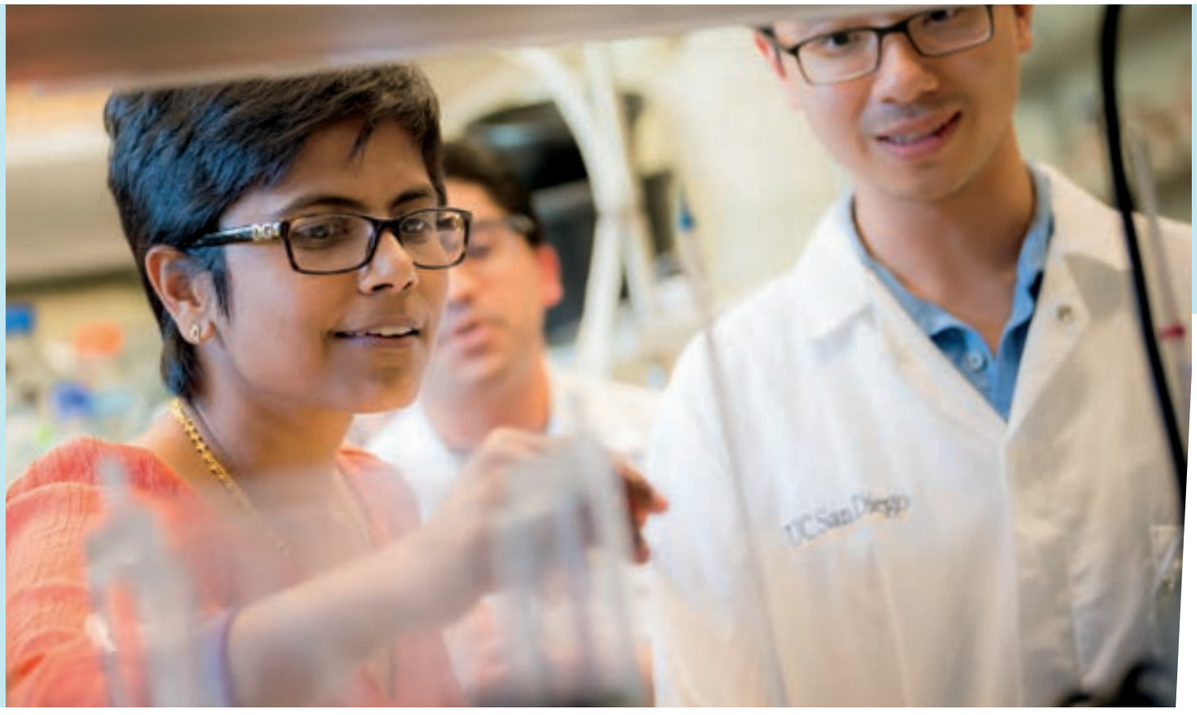
We want to catch this domino effect as early as we can in each person, but this is not something a doctor could ever do without AI," Ghosh said.

The team has already used this approach to advance understanding of numerous diseases, including inflammatory bowel disease, colorectal cancer, Kawasaki disease and COVID-19. In several proof-of-concept projects, researchers have successfully used algorithms to retroactively predict patients' diagnosis, prognosis and which treatments would work best.

In the case of inflammatory bowel disease, for example, the team was able to map out a network of genes involved in the disease, not only identifying which genes they were, but also grouping them into clusters to reveal which cellular process each group affects. They then used machine learning approaches to ask which part of this network was contributing most to the disease.

"An expert radiologist spends years and years reviewing clinical images, training their brain to identify these subtle visual signs of disease. An artificial neural network can learn them in hours."

ALBERT HSIAO, MD, PHD



"These algorithms are showing us things we've overlooked for years and truly changing the way we practice medicine."

PRADIPTA GHOSH, MD

"THE ANSWER SURPRISED US,"

SAID GHOSH. "EVERYONE WAS FOCUSED ON THE inflammation, but our algorithm said the most important thing was actually the integrity of the epithelial barrier lining the intestines."

The researchers then identified several gene targets critical to this part of the network.

"No one had considered these genes before, but when we reviewed previous clinical trials, the drugs that happen to affect this part of the biology were always the most successful." Multiple studies had even documented that the return of tight junctions in the epithelial barrier was the only true determinant of disease remission.

"These algorithms are showing us things we've overlooked for years, and truly changing the way we practice medicine."

Ghosh attributes much of their success to Sahoo's unique approach to AI. "What sets us apart is the underlying mathematical framework," she said. "Debashis has pioneered a new way of analyzing gene expression data that is optimized to find these fundamental features of health and disease."

Ghosh is so invested in this AI strategy that she's actually left her clinical practice to further focus on this work.

"It's just really hard to be in the clinic talking to a patient and describing all the things we know about their disease, but still having to say, 'I'm sorry, I don't have a drug for you today,'" Ghosh said. "I'm drawn to this work because it feels like a better way for me to have a true impact on these patients' lives."

SHINING LIGHT ON THE BLACK BOX

A COMPLEMENTARY EFFORT IN AI-DRIVEN disease prediction and drug discovery is taking place in the lab of **Trey Ideker, PhD**, professor of Medicine, Computer Science and Bioengineering at UC San Diego. Ideker's team collects genomic, proteomic and cellular imaging data to study diseases such as cancer and autism spectrum disorder and then analyzes the data with machine learning algorithms.

"If we want to understand what drugs work best on different kinds of tumors, for example, we can set up a thousand different tumor cell lines with different gene mutations and expose each to a thousand different drugs," Ideker said. "Suddenly we have a billion data points to train an algorithm on, instead of waiting on trial and error in human patients to figure out what works or doesn't."

This approach is useful for identifying putative drugs and also in refining their clinical trials.

"The same way your Netflix algorithm predicts what movie you should watch tonight, our algorithms will predict what drug is best fit to treat your cancer."

TREY IDEKER, PHD

"A clinical trial is much more likely to succeed if it's focused on people who have the genetic background or are at the stage of disease that the drug is most likely to benefit, as opposed to trying it on a broader population and having no idea why it worked on some people and didn't work on others," Ideker said. "Using AI to guide clinical trials allows the people who could benefit from the drug to get it sooner."

Like Ghosh, Ideker envisions a future in which AI tools are a critical component of the health care process.

"The same way your Netflix algorithm predicts what movie you should watch tonight, our algorithms will predict what drug is best fit to treat your cancer," he said.

So what's holding physicians back from using AI in this way now?

According to Ideker, one of the biggest issues is interpretability. Most AI algorithms currently function as "black boxes," meaning when they reach a conclusion about something, no one knows exactly how or why that decision was made. This makes it difficult for doctors and patients to trust the recommendations.

"It's not enough for an algorithm to just take a complex set of mutations and decide what drug to give a patient if we don't know why it's making that choice," said Ideker. "We may now have enough human genomes sequenced to power precision medicine, but what we don't have yet is a clear map of cellular biology to interpret the data with."

To address this, Ideker is leading a series of projects aimed at mapping the structure and function of various cell types, and using these models to inform the AI algorithms. Rather than remaining a "black box," Ideker's team constructs "visible" AI systems in which layers of the neural network are coupled to a hierarchy of cellular processes. The resulting algorithms not only report a drug recommendation but also allow physicians to see which molecular and cellular pathways informed that decision.

This approach recently received support from the National Institutes of Health (NIH) Bridge to Artificial Intelligence (Bridge2AI) program, for which Ideker serves as one of several leading principal investigators. Bridge2AI is NIH's largest and most direct investment in AI technology, aimed at advancing its widespread use in research and medicine. Ideker will lead one of four core projects designed to generate comprehensive AI-ready datasets that will lay the groundwork for new, interpretable and trustworthy AI technologies.

"WHILE OUR ALGORITHMS AREN'T THE ONES MAKING THE DECISIONS YET, IT'S EXCITING TO SEE THEM FINALLY HAVE A SEAT AT THE TABLE."

TREY IDEKER, PHD

TREY IDEKER, PHD

DEBASHIS SAHOO, PHD

It's not possible to conceive of precision medicine that doesn't use AI, and it's a big deal to have NIH recognize that in this way," Ideker said.

In the new multi-institutional project, Ideker and colleagues will attempt to map the components of a human cell in its entirety, starting with the most basic cell type: the stem cell.

The researchers will obtain induced pluripotent stem cells from a variety of genetic backgrounds and combine microscopy, biochemistry and computational tools to study their biology at multiple scales.

The final product will be a comprehensive model of the architecture of a human cell, from genes and proteins to entire organelles and how they work together. Once the stem cell has been modeled, they plan to use the same approach to model other cells, such as those that are dividing, differentiating or in various disease states.

Their goal is to eventually have a library of cell maps across many demographic and disease contexts, which could be used to train AI algorithms to make informed and interpretable decisions about human health.

"UC San Diego has proven itself to be a leader in clinical and research AI technology, but being part of Bridge2AI is going to be an enormous opportunity for us," Ideker said.

As he and others continue to lay the groundwork for future advances in biomedical AI, physicians have already begun to embrace their findings in the clinic. Ideker often consults with the tumor board at Moores Cancer Center, where his lab's research helps guide physicians in designing treatment plans.

"Every cancer patient first tries the established standard of care, but once you've gone through those initial options, physicians suddenly have a lot more freedom in what treatment strategies they can recommend," Ideker said. "While our algorithms aren't the ones making the decisions yet, it's exciting to see them finally have a seat at the table." ●

ORGAN MATCH

BY SCOTT LAFEE

AN ORGANOID IS NOT AN ORGAN, and that's a factoid, which looks a lot like a fact but isn't quite. Organoids are three-dimensional, artificially grown masses of cells that mimic specific organs or functions performed by those organs, but they don't do everything the actual organ does.

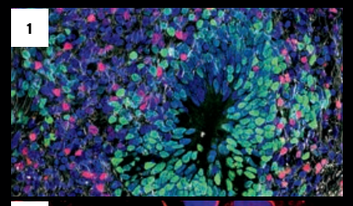
For example, a research team led by **Alysson Muotri, PhD**, a professor in the departments of Pediatrics and Cellular and Molecular Medicine in the UC San Diego School of Medicine, has created nine-month-old brain organoids that generate electrical signals similar to patterns produced in the developing brains of premature babies.

These brain organoids, which are roughly the size of sesame seeds, do not have the capabilities of fully developed brains, but they do represent a scientific advance that was once unthinkable, providing a new way to explore the human condition in unprecedented detail and complexity.

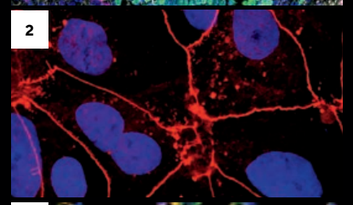
In recent years, scientists at UC San Diego and elsewhere have learned how to build organoids mimicking many different organs and their biological functions, including the lungs and the gut. ●

Can you match the numbered micrographs of different organoids with their research descriptions?

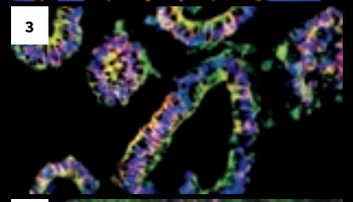
1



2



3



4

Answers: A-2, B-1, C-3, D-4

A

Mini-gut organoids, developed by **Pradipta Ghosh, MD**, professor of cellular and molecular medicine, and **Soumita Das, PhD**, associate professor of pathology, with colleagues at the HUMANOID Center of Research Excellence, are being used to explore the molecular system that keeps intestinal linings sealed. The knowledge might help prevent a condition known as "leaky gut," in which microbes and other molecules seep out into the body, where they can trigger an adverse immune response and contribute to a variety of conditions, from inflammatory bowel disease to arthritis.

B

Muotri and colleagues are using brain organoids to investigate how the human brain develops and has evolved, plus a wide range of neurological ailments. His research has produced brain organoids that mimic autism spectrum disorder, differences between the brains of Neanderthals and modern *Homo sapiens* and how infection by the Zika virus causes birth defects, such as microcephaly (an undersized head and brain). Brain organoids have even been sent into space to chronicle how they develop in the absence of gravity.

C

Though COVID-19 is primarily regarded as a respiratory disease, the SARS-CoV-2 virus can infect the brain. **Tariq Rana, PhD**, Distinguished Professor in the Department of Pediatrics, and colleagues have compared how the virus affects different parts of the body differently using lung and cerebral organoids.

D

Karl Wahlin, PhD, assistant professor of ophthalmology and director of the Richard C. Atkinson Laboratory for Regenerative Ophthalmology at Shiley Eye Institute, uses human pluripotent stem cell derived mini-retinas to explore human retinal development and disease. CRISPR gene-edited stem cells with fluorescent proteins integrated in retinal genes provide a useful means to explore retinal cells upon differentiation. Retinas of other species, such as amphibians, fish and birds, are being studied to better understand their abilities to self-repair damage — a capability lost or dramatically reduced in higher mammals. Human retinal organoids are also being used to explore retinal repair in humans, with the goal being to restore vision.

UC San Diego
HEALTH SCIENCES